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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ALAN L. EPSTEIN, JIALI LI,
and PEISHENG HU

Appeal 2011-006369
Application 11/674,569
Technology Center 1600

Before TONI R. SCHEINER, DEMETRA J. MILLS, and JOHN G. NEW,
Administrative Patent Judges.

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-3, 5-11, 14-23, and 47-71, directed to a method of inhibiting cancer cells. The Examiner has rejected the claims on the grounds of anticipation and obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 1-3, 5-11, 14-23, and 47-71 are pending and on appeal.
Claims 12 and 13 have been withdrawn from consideration, and claims 4
and 24-46 have been canceled (App. Br. 2).

Claims 1, 2, 11, 18, and 19 are representative:

1. A method of reducing the size of a tumor or inhibiting the growth of cancer cells in an individual, consisting essentially of administering an effective amount of a cancer therapeutic agent comprising a cancer targeting molecule linked to a liver-expressed chemokine (LEC) to the individual wherein said cancer therapeutic agent can target to cancer cells or tumor in vivo and said LEC functions as a chemoattractant for monocytes, lymphocytes, or polymorphonuclear leukocytes.
2. A method according to claim 1 further consisting essentially of reducing the activity of immunoregulatory T cells in the individual.
11. A method according to claim 1, wherein said cancer targeting molecule is an antibody.
18. A method according to claim 1 wherein said cancer targeting molecule is a protein linked to LEC by genetic fusion.
19. A method according to claim 18 wherein LEC is fused at its C-terminus to the N-terminus of said cancer targeting molecule.

In response to a requirement for election of species, Appellants elected the humanized monoclonal antibody NHS76 as the cancer targeting molecule (Appellants' Response of June 4, 2009).

The Examiner relies on the following evidence:

Vicari et al	US 2003/0138413 A1	Jul. 24, 2003
Brenner et al.	US 2003/0148982 A1	Aug. 7, 2003
Williams et al.	WO 00/01822 A1	Jan. 13, 2000

James J. Mulé et al., *The Anti-Tumor Efficacy of Lymphokine-Activated Killer Cells and Recombinant Interleukin 2 in Vivo: Direct Correlation Between Reduction of Established Metastases and Cytolytic Activity of Lymphokine-Activated Killer Cells*, 136 J. IMMUNOL. 3899-3909 (1986).

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Shozaburo Onizuka et al., *Tumor Rejection by in Vivo Administration of Anti-CD25 (Interleukin-2 Receptor α) Monoclonal Antibody*, 59 CANCER RESEARCH 3128-3133 (1999).

Appellants rely, in relevant part, on the following additional evidence:

Jiali Li et al., *Complete Regression of Experimental Solid Tumors by Combination LEC/chTNT-3 Immunotherapy and CD25⁺ T-Cell Depletion*, 63 CANCER RESEARCH 8384-8392 (2003).

Declaration of Dr. Alan Epstein, submitted under 37 C.F.R. § 1.132, dated December 23, 2005 (“Epstein Decl.”).

Declaration of Dr. Manuel Penichet, submitted under 37 C.F.R. § 1.132, dated January 4, 2007 (“Penichet Decl.”).

The claims stand rejected as follows:

I. Claims 1, 11, 17, 18, and 21-23 under 35 U.S.C. § 102(e) as anticipated by Vicari.

II. Claims 1-3, 5-8, 17-23, 47-52, 54-64, and 69-71 under 35 U.S.C. § 103(a) as unpatentable over Vicari and Onizuka.

III. Claims 1, 11, 14-23, 53, 61, and 64-68 under 35 U.S.C. § 103(a) as unpatentable over Vicari and Williams.

IV. Claims 1, 9, 10, and 17-23 under 35 U.S.C. § 103(a) as unpatentable over Vicar, Mulé and Brenner.

We affirm-in-part.

FINDING OS FACT

1. Vicari discloses a method of treating cancer in a mammal comprising administering a tumor-derived dendritic cell inhibitory factor (TDDCIF) antagonist in combination with a Toll-like receptor (TLR) agonist (Vicari ¶¶ 10-12).

2. In addition, Vicari discloses administering a chemokine, including the liver-expressed chemokine, CCL16, “via a targeting construct”

(Vicari ¶ 18), which includes an antibody that “recognizes or targets a tumor-associated antigen” (*id.* at ¶ 74), “either before or concurrently, with the tumor-derived DC inhibitory factor antagonist and/or TLR agonist” (*id.* at ¶ 18).

3. Claim 1 is directed, in relevant part, to a method “consisting essentially of” administering a cancer therapeutic agent comprising a cancer targeting molecule linked to a liver-expressed chemokine (LEC) to an individual, wherein the cancer therapeutic agent targets cancer cells *in vivo* and the “LEC functions as a chemoattractant for monocytes, lymphocytes, or polymorphonuclear leukocytes.” Similarly, the Specification teaches that the cancer therapeutic agent comprises a “cancer targeting molecule,” e.g., an antibody specific for an intracellular tumor antigen like chTNT-3 or NHS76, linked to a liver-expressed chemokine (LEC), e.g., CCL16. According to the Specification, the cancer targeting molecule “has the ability to localize to cancer cells *in vivo*” (Spec. ¶ 26), while the LEC “is a potent chemotactic factor for both human monocytes and dendritic cells (APC cells)” (*id.* at ¶ 45), as well as “CD8⁺ lymphocytes and polymorphonuclear leukocytes” (*id.* at ¶ 46; *see also* ¶ 113).

4. According to the Specification, “in each instance herein any of the terms ‘comprising,’ ‘consisting essentially of’ and ‘consisting of’ may be replaced with either of the other two terms” (Spec. ¶ 118).

5. Example 4 of the Specification demonstrates that treatment of groups of tumor-bearing mice with a tumor-targeting LEC/chTNT-3 fusion protein resulted in a 55% ($p \leq 0.05$) tumor growth reduction in a Colon 26

tumor model, a 37% ($p \leq 0.05$) reduction in a MADI09 tumor model, and a 42% ($p \leq 0.05$) reduction in a RENCA tumor model as compared to untreated controls (Spec. ¶¶ 107, 108).

In addition, Example 5 demonstrates that when $CD4^+CD25^+$ T-cells were depleted in combination with administration of control antibody chTNT-3, “Colon 26 tumors showed impressive reduction in tumor growth about as much as LEC/chTNT-3 alone” (*id.* at ¶ 115). However, neither of these treatment groups were cured of their implanted tumors, and “[c]omplete and lasting remissions were not obtained until $CD4^+CD25^+$ T-cell depletion was performed in combination with LEC/chTNT-3” (*id.*).

6. In addition, Declarant Dr. Alan Epstein attests that:

[A]ntibody fusion proteins prepared with IL-2, IFN- γ or GM-CSF are unable to achieve cancer cures *in vivo* when linked to antibodies reactive with tumor associated antigens, even when this approach is combined with CD25(+) T-cell depletion. See, e.g., Li et al., *Cancer Res.* 2003 Dec 1; 63(23):8384-92 (of record in this case). Quite surprisingly, cancer therapeutic agents comprising a cancer targeting antibody fused to LEC are significantly superior to conjugates prepared with other cytokines, achieving complete regression of experimental solid tumors when combined with CD25(+) T-cell depletion. This is demonstrated in the instant patent application and in Li et al. *Cancer Research* article.

(Epstein Decl. ¶ 8.)

7. Li teaches, in relevant part,

The depletion of $CD25^+$ T-cells . . . dramatically decreased the tumor growth by 70% and 60% in Colon 26 . . . and RENCA . . . models, respectively. These results were similar to that seen with LEC/chTNT-3 treatment alone. However, the combination of LEC/chTNT-3 immunotherapy and [$CD4^+$ $CD25^+$] depletion caused complete remission of these well-established tumors for up to 6 months.

(Li 8387, col. 1.)

On the other hand, “[s]ubstitution of LEC/chTNT-3 with three different chTNT-3/cytokine [IL-2, IFN- γ or GM-CSF] fusion proteins when used in combination with CD4⁺ depletion did not produce complete remissions in the Colon 26 tumor model” (*id.* at 8387, col. 2).

ANTICIPATION

I.

Claims 1, 11, 17, 18, and 21-23 stand rejected as anticipated by Vicari. The claims have not been separately argued with respect to this rejection (App. Br. 5, 24). We select claim 1 as representative, and the remaining claims will stand or fall accordingly. 37 C.F.R. § 41.37(c)(1)(vii).

Principles of Law

“By using the term ‘consisting essentially of,’ the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.” *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998).

[C]laims are given their broadest reasonable construction consistent with the specification. . . . [A]n applicant who has not clearly limited his claims is in a weak position to assert a narrow construction. Therefore, in construing the phrase ‘consisting essentially of’ in appellants’ claims, it is necessary and proper to determine whether their specification reasonably supports a construction that would include [or exclude] additives such as [those in the prior art].

In re Herz, 537 F.2d 549, 551 (CCPA 1976).

Discussion

The Examiner finds that Vicari discloses a method of treating cancer by administering a linked “tumor targeting agent and a chemokine, such as CCL16, known as LEC (SEQ ID NO:3)” (Ans. 4, 15).

Appellants contend that claim 1 is directed to a method “consisting essentially of administering . . . a cancer chemotherapeutic agent comprising a cancer targeting molecule linked to a liver-expressed chemokine (LEC)” (App. Br. 6).

Appellants contend that Vicari is principally directed to “facilitating the activation of tumor-infiltrating dendritic cells (DC) by administering a tumor-derived DC inhibitory factor (TDDCIF) antagonist in combination with . . . a Toll Like Receptor (TLR) agonist” (*id.* at 7), in order to “improve[] tumor antigen-specific immune responses” (*id.*). Appellants do not dispute the Examiner’s finding that Vicari discloses administration of an LEC-tumor targeting antibody construct, but contend that administration of the construct is merely an adjunct to administration of the TDDCIF antagonist and TLR agonist (*id.* at 8).

According to Appellants, the Specification demonstrates that “administering a cancer targeting molecule linked to a LEC is sufficient to reduce tumor size in a mouse tumor model” (*id.* at 7), thus, Vicari’s administration of a TDDCIF antagonist and a TLR agonist “would be excluded by the transition term ‘consisting essentially of’ because the inclusion of these active agents would materially affect the basic and novel characteristics of the claimed method” (*id.* at 9).

Appellants’ argument is not persuasive. The Specification teaches that the cancer therapeutic agent comprises a “cancer targeting molecule,”

e.g., an antibody specific for an intracellular tumor antigen, linked to a liver-expressed chemokine (LEC), e.g., CCL16. As discussed above, the Specification teaches that the cancer targeting molecule has the ability to localize to cancer cells *in vivo*, while the LEC is a potent chemotactic factor for human monocytes, dendritic cells, lymphocytes and polymorphonuclear leukocytes (FF3). Appellants have not established that administration of a TDDC1F antagonist and/or a TLR agonist would somehow prevent the antibody-LEC construct from functioning in this manner. In any case, Vicari teaches that the construct can be administered *before* the TDDC1F antagonist and TLR agonist (FF2).

Moreover, claim 1 is clearly open to additional steps (*see, e.g.*, dependent claims 2, 3, 9, and 10), despite the transitional phrase “consisting essentially of,” and Appellants have not identified anything in the Specification that explicitly excludes administration of a TDDC1F antagonist and a TLR agonist. Finally, the Specification explicitly states that the terms “comprising” and “consisting essentially of” may be replaced by each other - that is, the terms are interchangeable (Spec. ¶ 118; FF4).

Therefore, we find no factual or legal basis to support the assertion that Vicari’s TDDC1F antagonist and TLR agonist would materially affect the basic and novel characteristics of the claimed method, and we agree with the Examiner that the claims do not exclude administration of Vicari’s TDDC1F antagonist and TLR agonist. *See PPG*, 156 F.3d at 1354; *Herz*, 537 F.2d at 551.

The rejection of claim 1 as anticipated by Vicari is affirmed. Claims 11, 17, 18, and 21-23 were not separately argued, and fall with claim 1.

OBVIOUSNESS

II.

Claims 1-3, 5-8, 17-23, 47-52, 54-64, and 69-71 stand rejected as unpatentable over Vicari and Onizuka.

The Examiner relies on Vicari as discussed above, but acknowledges that Vicari does not teach “depleting immunoregulatory T cell[s] with an antibody to IL-2 receptor or CD25” (Ans. 7). However, the Examiner finds that Onizuka teaches that CD25⁺ T cells inhibit immunity (*id.* at 8), and that “depletion of this population of T cell[s] by in vivo (ex vivo) administration of antibody to CD25 causes tumor regression” (*id.* at 7).

The Examiner concludes that it would have been obvious for one of ordinary skill in the art “to further include the method of Onizuka in the methods of Vicari . . . in order to increase the efficacy and benefit for the cancer treatment” (*id.* at 7-8).

Appellants contend that “the compositions and methods required in Vicari materially affect the basic and novel characteristics of the claimed invention, [thus] Vicari does not teach a cancer therapeutic agent consisting essentially of a cancer targeting molecule that can target to cancer cells or tumor *in vivo*” (App. Br. 17). Appellants further contend that “Onizuka is not concerned with chemokines generally, or their use as anti-cancer agents . . . [and] therefore fails to correct the deficiency of Vicari” (*id.*).

These arguments are not persuasive. As discussed above, we find no factual or legal basis to support the assertion that Vicari’s TDDC1F antagonist and TLR agonist would materially affect the basic and novel characteristics of the claimed method, and we agree with the Examiner that the claims do not exclude administration of Vicari’s TDDC1F antagonist and TLR agonist. Moreover, the Examiner has explained why one of ordinary

skill in the art would have had reason to deplete immunoregulatory CD25⁺ T-cells, but Appellants have not directly addressed the Examiner's rationale for combining Onizuka with Vicari.

However, Appellants further contend that the Specification and the Epstein and Penichet Declarations establish that "the inventors have surprisingly discovered that cancer therapeutic agents comprising a cancer targeting agent fused to LEC are significantly superior to . . . [IL-2, IFN, GM-CSF] conjugates, being less toxic and achieving complete regression of experimental solid tumors when combined with CD25(+) T-cell depletion" (*id.* at 19).

Essentially, the Examiner's position is that "[c]ombining two known methods for treating the same disease with the same materials would achieve the same or additive result and would not be unexpected" (Ans. 20).

Nevertheless, the Examiner has not addressed Appellants' evidence purporting to show that administration of LEC/chTNT-3 alone results in tumor growth reduction, as does CD25⁺ T-cell depletion alone, but "[c]omplete and lasting remissions were not obtained until CD4⁺CD25⁺ T-cell depletion was performed in combination with LEC/chTNT-3" (Spec. ¶ 115; FFs 5-7) - a result that is seemingly neither the same as either strategy alone, nor merely additive, i.e., seemingly a difference in kind, rather than degree.¹

¹ *See In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) (citations omitted): "[E]ven though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable . . . unless the claimed ranges "produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art."

The Examiner has not adequately addressed Appellants' assertion of unexpected results for those claims which require the additional step of reducing the activity of immunoregulatory cells. Accordingly, the rejection of claims 2, 3, 5-8, 47-60, 62, 63, and 69-71 as unpatentable over Vicari and Onizuka is reversed. However, the rejection of claims 1, 17-23, 61, and 64 as unpatentable over Vicari and Onizuka is affirmed as none of these claims requires this additional step.

III.

Claims 1, 11, 14-23, 53, 61, and 64-68 stand rejected as unpatentable over Vicari and Williams.

According to the Examiner, "the cancer targeting agent in [these] claims is examined to the extent of the [elected] NHS76 antibody" (Ans. 5). The Examiner relies on Vicari as discussed above, but acknowledges that Vicari does not teach "LEC fused to . . . the specific antibody NHS76" (*id.* at 6). However, the Examiner cites Williams as disclosing the antibody NHS76, which is humanized "for the purpose of treating human patients" (*id.*), and which "binds an intracellular antigen" in tumors (*id.*). In addition, the Examiner finds that Vicari discloses general conjugation strategies for antibodies and various factors (*id.* at 7).

The Examiner concludes that it would have been obvious to substitute the humanized NHS76 antibody for another antitumor antibody in Vicari's LEC construct "in order to increase . . . the efficacy of in vivo tumor treatment" (*id.*). In addition, the Examiner concludes that it would have been obvious "to make the conjugate of LEC fused at its C- or N-terminus of the light or heavy chain of the NHS76 antibody because Vicari et al have shown a method of making the conjugate" (*id.*).

Appellants reiterate that “the compositions and methods required in Vicari materially affect the basic and novel characteristics of the claimed invention, [thus] Vicari does not teach a cancer therapeutic agent consisting essentially of a cancer targeting molecule that can target to cancer cells or tumor *in vivo*” (App. Br. 16). Appellants further contend that “Williams is not concerned with chemokines generally, or their use as anti-cancer agents . . . [and] therefore fails to correct the deficiency of Vicari” (*id.*).

Appellants’ arguments are not persuasive. Again, we find no factual or legal basis to support the assertion that Vicari’s TDDCIF antagonist and TLR agonist would materially affect the basic and novel characteristics of the claimed method, and we agree with the Examiner that the claims do not exclude administration of Vicari’s TDDCIF antagonist and TLR agonist. Moreover, to the extent the claims require the elected antibody NHS76, the Examiner has provided a fact based explanation for why one of ordinary skill in the art would have had reason to use this antibody in Vicari’s construct, but Appellants have not addressed this issue in any way.

Appellants further contend that Vicari and Williams fail to “disclose the feature that LEC is fused to the C-terminus of a cancer targeting molecule as required by claim 19 or fused to the N-terminus of the light or heavy chain of an antibody as required by claim 20 . . . [which] further undermine[s] the Examiner’s prima facie case of obviousness” (*id.* at 27).

We are not persuaded. Again, the Examiner has explained why one of ordinary skill in the art would have found it obvious to link the LEC and the antibody as specified. It is not enough for Appellants to state that the references do not explicitly disclose it.

Nor are we persuaded by Appellants' contention that the Specification and the Epstein and Penichet Declarations establish that "the inventors have surprisingly discovered that cancer therapeutic agents comprising a cancer targeting agent fused to LEC are significantly superior . . . when combined with CD25(+) T-cell depletion" (App. Br. 19, 25) , as none of these claims requires CD25⁺ T-cell depletion, with the exception of claim 53.

Accordingly, we affirm the rejection of claims 1, 11, 14-23, 61, and 64-68 as unpatentable over Vicari and Williams, but reverse with respect to claim 53 (for the reasons discussed above in connection with the rejection over Vicari and Onizuka).

IV.

Claims 1, 9, 10, and 17-23 stand rejected as unpatentable over Vicari, Mulé and Brenner.

The Examiner relies on Vicari as discussed above, but acknowledges that Vicari does not teach the "additional step of administering active cytotoxic T cell[s]" (Ans. 8). However, the Examiner cites Mulé and Brenner as disclosing "adoptive immunotherapy for tumor treatment by administering in vitro activated T-cells" (*id.*). The Examiner concludes that it would have been obvious to administer in vitro modified or activated cytotoxic T cells to Vicari's subjects because Mulé and Brenner have "shown that in vitro modification or activation of T cells increases the population and cytotoxic activity of the T cell in vivo" (*id.* at 9).

Again, Appellants contend that "the compositions and methods required in Vicari materially affect the basic and novel characteristics of the claimed invention, [thus] Vicari does not teach a cancer therapeutic agent consisting essentially of a cancer targeting molecule that can target to cancer

cells or tumor *in vivo*” (App. Br. 18). Appellants further contend that neither Mulé nor Brenner “is concerned with chemokines generally, or their use as anti-cancer agents . . . [and] therefore fail to correct the deficiency of Vicari” (*id.*).

Appellants’ arguments are not persuasive. As discussed above, we find no factual or legal basis to support the assertion that Vicari’s TDDCIF antagonist and TLR agonist would materially affect the basic and novel characteristics of the claimed method, and we agree with the Examiner that the claims do not exclude administration of Vicari’s TDDCIF antagonist and TLR agonist. Moreover, to the extent the claims require the additional administration of active cytotoxic T cells, the Examiner has provided an explanation for why one of ordinary skill in the art would have had reason to do so, but Appellants have not addressed this issue in any way.

Finally, to the extent Appellants contend that the Specification and the Epstein and Penichet Declarations establish that “the inventors have surprisingly discovered that cancer therapeutic agents comprising a cancer targeting agent fused to LEC are significantly superior . . . when combined with CD25(+) T-cell depletion” (App. Br. 19), we are not persuaded. Again, none of these claims requires CD25⁺ T-cell depletion.

The rejection of Claims 1, 9, 10, and 17-23 as unpatentable over Vicari, Mulé and Brenner is affirmed.

SUMMARY

I. The rejection of claims 1, 11, 17, 18, and 21-23 as anticipated by Vicari is affirmed.

II. The rejection of claims 1-3, 5-8, 17-23, 47-52, 54-64, and 69-71 as unpatentable over Vicari and Onizuka is affirmed with respect to

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claims 1, 17-23, 61, and 64, and reversed with respect to claims 2, 3, 5-8, 47-60, 62, 63, and 69-71.

III. The rejection of claims 1, 11, 14-23, 53, 61, and 64-68 as unpatentable over Vicari and Williams is affirmed with respect to claims 1, 11, 14-23, 61, and 64-68, and reversed with respect to claim 53.

IV. The rejection of claims 1, 9, 10, and 17-23 as unpatentable over Vicar, Mulé and Brenner is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc