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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MATHEW L. THAKUR and LEONARD G. GOMELLA

Appeal 2019-006573
Application 14/767,936
Technology Center 1600

Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and MICHAEL A. VALEK, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 5–12, 14, and 16–18 (Appeal Br. 3). We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as "Thomas Jefferson University" (Appellant's April 12, 2019 Appeal Brief (Appeal Br.) 1).

STATEMENT OF THE CASE

Appellant's disclosure:

> [P]rovides methods for detecting shed or circulating tumor cells and diagnosing cancer by contacting a biological fluid with a labeled pituitary adenylate cyclase activating peptide (PACAP) or vasoactive intestinal peptide (VIP), and determining binding of the PACAP or VIP to shed or circulating tumor cells in the biological fluid. In one embodiment, the biological fluid is blood, urine or cerebrospinal fluid.

(Spec. ¶ 7.) Claim 5 is reproduced below:

> 5. A method for detecting shed or circulating tumor cells that overexpress a pituitary adenylate cyclase activating peptide (PACAP) receptor comprising:
>
> (a) contacting a biological fluid obtained from a subject with a labeled PACAP having a label;
>
> (b) detecting binding of the labeled PACAP to shed or circulating tumor cells in the biological fluid; and
>
> (c) comparing binding of the labeled PACAP to shed or circulating tumor cells in the biological fluid to binding or lack of binding of labeled PACAP in a control sample thereby detecting shed or circulating tumor cells.

(Appeal Br. 21.)

Grounds of rejection before this Panel for review:[2, 3]

Claims 16 and 17 stand rejected under 35 U.S.C. 112(b).

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[2] Examiner withdrew the Final rejections under 35 U.S.C. § 101 and the written description provision of 35 U.S.C. § 112(a) (Examiner's July 5, 2019 Answer (Ans.) 3).

[3] Office records indicate that Application 14/767,927 abandoned February 19, 2020. Therefore, the provisional nonstatutory double patenting rejection over the claims of this Application is moot and will not be discussed further.

Claims 5–12, 14, 16–18 stand rejected under 35 U.S.C. § 103 as unpatentable over the combination of Thakur '133,[4] Dong,[5] Russell,[6] and Fujita.[7]

Claims 5–12, 14, 16–18 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–17 of Thakur '308,[8] in view of Thakur '133, Dong, Russell, and Fujita.

DEFINITENESS:

ISSUE

Does the preponderance of evidence support Examiner's conclusion that Appellant's claims 16 and 17 are indefinite?

ANALYSIS

Examiner finds that Appellant's claims 16 and 17 "depend on a canceled claim" and "[t]herefore, their metes and bounds are indefinite" (Ans. 9). Appellant "propose[s] to address this rejection by amending claims 16–17 to depend from claim 5" (Appeal Br. 20). Because Appellant's proposed amendment was not made, the rejection is sustained (*see* Ans. 23 (Examiner finds that "the proposed amendments have not yet been made")).

[4] Thakur, US 2003/0129133 A1, published July 10, 2003.
[5] Dong, WO 00/05260, published Feb. 3, 2000.
[6] Russell et al., US 5,861,248, issued Jan. 19, 1999.
[7] Fujita, et al., *Specific detection of prostate cancer cells in urine by multiplex immunofluorescence cytology*, 40 Hum. Pathol. 924–33 (2009).
[8] Thakur, US 6,855,308 B2, issued Feb. 15, 2005.

CONCLUSION

The preponderance of evidence supports Examiner's conclusion that Appellant's claims 16 and 17 are indefinite. The rejection of claims 16 and 17 under 35 U.S.C. 112(b) is affirmed.

For the purposes of this Opinion, we review the rejections of Appellant's claims 16 and 17 under obviousness and obviousness-type double patenting as if both claims depended from Appellant's claim 5.

OBVIOUSNESS:

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. Thakur '133 relates "to the use of radiolabeled PACAP and biologically active PACAP fragments and analogs for imaging or therapy of breast and other tumors which express PACAP, VIP-R1 and VIP-R2 receptors. PACAP, VIP-R1 and VIP-R2 receptors are hereinafter collectively referred to as 'VPAC receptors'" (Thakur '133 ¶ 16; *see id*. at Abstract (Thakur '133 discloses that "[t]umors expressing VPAC receptors can be imaged or treated with compounds comprising PACAP, or a biologically active PACAP fragment or analog"); *see also* Ans. 4).

FF 2. Thakur '133 discloses that "VPAC receptors . . . are expressed in high density on breast tumor . . . and other tumor cells," including "ovarian, endometrial, prostate, bladder, lung, esophageal, colonic, pancreatic, neuroendocrine and brain tumors" (Thakur '133 ¶ 13; *see also* Ans. 4).

FF 3. Thakur '133

> provides a method of detecting tumors expressing VPAC receptors, comprising administering an effective amount of an imaging compound of formulae A or B to a subject who has, or is suspected of having, such a tumor. After administration of the imaging compound, a scintigr[a]phic image is generated of at least part of the subject's body.

(Thakur '133 ¶ 17; *id.* ¶ 90 (Thakur '133 discloses that in practice, "an effective amount of an imaging compound comprising PACAP, or a biologically active PACAP fragment or analog, is administered to a subject by any suitable enteral or parenteral route of administration."); *id.* ¶ 94 (Thakur '133 discloses that "[a]fter the imaging compound is administered to the subject, a scintigr[a]phic image is generated of at least part of the subject. For example, an image is desirably obtained of that part of the subject's body containing, or which is suspected of containing, the tumor."); *see also* Ans. 4.)

FF 4. Thakur '133 discloses that "[a] compound . . . comprising PACAP, or a biologically active PACAP fragment or analog, and an imaging radionuclide is an 'imaging compound'" (Thakur '133 ¶ 87; *see generally* Ans. 4–5).

FF 5. Examiner relies on Dong to disclose PACAP analogues (*see* Ans. 5; *see also* (Dong 1:5–7 (Dong "is directed to novel analogues of PACAP . . . and the use thereof for treating . . . conditions and[/]or diseases"); Dong 8:18–31 (Dong discloses a variety of conditions and diseases that may be treated with its PACAP analogues)).

FF 6. Examiner finds that the combination of Thakur '133 and Dong fail to suggest the "detection of circulating tumor cells in [a biological fluid, such as] urine" (Ans. 5).

FF 7. Russell discloses "a method for identification of prostate cancer cells in a biological sample[, such as urine,] by amplifying and detecting nucleic acids corresponding to prostate cancer cell markers" (Russell 28:15–26; *see id*. at Abstract (Russell "relates particularly to probes and methods for evaluating the presence of RNA species that are differentially expressed in prostate cancer compared to normal human prostate or benign prostatic hyperplasia"); *id.* at 40:35–43:29 (Russell exemplifies the "Identification of Markers of Prostate Disease by Use of RNA Fingerprinting); *see also* Ans. 6).

FF 8. Fujita discloses that "[i]t is known that prostate cancer cells are shed into biological fluids, particularly when the prostate is subjected to physical manipulation, thus creating the potential for their non-invasive detection in wither urine or expressed prostatic fluid" (Fujita § 1; *see* Ans. 6–7).

FF 9. Fujita discloses the detection of prostate cancer cells in urine (Fujita, Abstract; *see id*. §§ 2.2–4 (Fujita discloses an immunofluorescence assay to detect prostate cancer cells in urine); *id.* § 4 (Fujita discloses that "more prostate cancer-specific markers will [certainly] be developed over the coming years" and that "it will be of interest to optimize and study the most specific of these in such cohorts as well as in larger groups of men being screened and subsequently biopsied."); *see also* Ans. 6).

FF 10. Thakur declares that "[s]hed or circulating tumor cells are quite distinct from the cells of a primary tumor" (Thakur Decl.[9] ¶ 2 (citing Pantel[10] 1216 and Fig. 1) (Thakur relies on Pantel to "teach that tumor cells

[9] Declaration of Mathew L. Thakur, signed May 16, 2018.
[10] Pantel et al., *The biology of circulating tumor cells*, 35 Oncogene 1216–1224 (2016).

undergo a number of biological processes during . . . [circulating tumor cell (CTC)]-based *metastasis*) (emphasis added)).

FF 11. Thakur declares that "CTCs . . . exhibit numerous changes in gene expression after leaving the primary tumor" (Thakur Decl. ¶ 3 (citing LaTulippe,[11] Abstract) (Thakur relies on LaTulippe to "teach that the expression of more than 3000 tumor-intrinsic genes differ by at least 3-fold between primary prostate cancers and *metastatic* prostate cancers") (emphasis added)).

FF 12. Thakur declares that each of Dong, Thakur '133, Russell, and Fujita would not have provided a person of ordinary skill in this art with the necessary guidance to utilize a labeled PACAP to detect VPAC1 receptors expressed on shed or circulating tumor cells in an isolated biological sample, such as urine (Thakur Decl. ¶¶ 4–8).

FF 13. Thakur declares that "[a]s one having ordinary skill in the art, [Thakur] find[s] that the assays of the cited prior art are so incongruent that the ordinary artisan simply would not have sought these references out and combined the same to arrive at the claimed method" (Thakur Decl. ¶ 9).

ANALYSIS

Thakur '133 establishes that labeled PACAP can be used to detect and treat cells in vivo (*see* FF 1–4; *see generally* FF 5 (Dong discloses PACAP analogues)). Examiner appreciates that the combination of Thakur '133 and Dong fails to suggest the "detection of circulating tumor cells in [a biological fluid, such as] urine" (FF 6). Examiner finds, however, that

[11] LaTulippe et al., *Comprehensive Gene Expression Analysis of Prostate Cancer Reveals Distinct Transcriptional Programs Associated with Metastatic Disease*, 62 Cancer Research 4499–4506 (2002).

Russell and Fujita disclose methods of detecting prostate cancer cells in a biological sample, such as urine (*see* FF 7–9). In this regard, Fujita discloses a binding assay, i.e. immunoassay, to detect prostate cancer cells that are shed into urine in response to physical manipulation of the prostate (*see* FF 8–9). In addition, Fujita discloses that more in vitro assays using newly discovered prostate cancer markers will be developed, thus, providing a reasonable expectation of success in the use of additional, i.e. newly discovered, probes to optimize in vitro assays (*see* FF 9). *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success."). Thus, based on the combination of Thakur '133, Dong, Russell, and Fujita, we find no error in Examiner's conclusion that, at the time Appellant's invention was made, it would have been prima facie obvious to use labeled PACAP in a binding assay to detect prostate cancer cells that are shed into urine in response to physical manipulation of the prostate (*see generally* Ans. 6–7). In this regard, Fujita's disclosure of an interest in optimizing assays with newly developed probes (*see* FF 9), such as those disclosed by Thakur '133 (*see* FF 1–4), provides the reasonable expectation of success supporting Examiner's conclusion on this record.

Appellant relies on the Thakur Declaration and the evidence cited therein to support a contention that "there is no evidence of record to suggest that shed or circulating tumor cells (CTCs) retain expression of PACAP receptors once the cells are no longer associated with the primary tumor" (Appeal Br. 14; *see also* Reply Br. 2–3; FF 10–12). We are not persuaded. The evidence relied upon by Thakur makes clear that Thakur's statements

relates to cells shed as a result of CTC-based metastasis (*see* FF 10–11; *cf.* Ans. 19 (Examiner finds that "Fujita makes clear . . . the prostate cancer cells can be found in urine after physical manipulation of the prostate. Therefore, no metastasis is required."); *see also* FF 8–9; Appeal Br. 13–14 (Appellant appreciates that Fujita discloses, *inter alia*, "[i]t is known that prostate cancer cells are shed into biological fluids, particularly when the prostate is subjected to physical manipulation")). Stated differently, because Fujita's cells are obtained from physical manipulation of the prostate and not from metastasis, a person of ordinary skill in the art would not have expected these cells to differ from the primary tumor. In this regard, we note that Appellant failed to provide an evidentiary basis on this record to support a contrary conclusion. Therefore, we are not persuaded by Appellant's contention that because

> the cited prior art provides no evidence to demonstrate that PACAP receptor expression on the cell surface is retained once the shed . . . cancer cells leave the primary tumor, there can be no reasonable expectation that these cells can be detected based upon the combined teachings of the cited references.

(Appeal Br. 15.)

For the foregoing reasons, we are not persuaded by Appellant's contention that "Examiner has not provided evidence showing that a person of ordinary skill in the art would have had a reasonable expectation of success in replacing" the binding molecule, i.e. antibody, in Fujita's binding assay with the labeled binding molecule, i.e. PACAP peptide, taught by both of Thakur '133 and Dong (Appeal Br. 16; *see also* Reply Br. 3–4; FF 12). As Examiner explains, obviousness does not require an absolute predictatiblity of success, only a reasonable expectation of success, which,

on this record, is provided by the combination of Thakur '133, Dong, Russell, and Fujita (Ans. 17–18). *See O'Farrell*, 853 F.2d at 903.

Two criteria have evolved for determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved. *In re Clay*, 966 F.2d 656, 658–9 (Fed. Cir. 1992). On this record, Thakur '133, Dong, Russell, and Fujita relate to the use of binding molecules, including PACAP, to, *inter alia*, detect cells, including tumor cells (*see* FF 1–9). Thus, we find that Thakur '133, Dong, Russell, and Fujita are reasonably pertinent to the particular problem with which the inventor is involved. *See Clay*, 966 F.2d at 658–9. Therefore, we are not persuaded by Appellant's contention that Thakur '133, Dong, Russell, and Fujita are non-analogous art (*see* Appeal Br. 15–16; *see also* Reply Br. 4–5; FF 13).

For the foregoing reasons, we are not persuaded by Appellant's contention that Examiner relied on impermissible hindsight (Appeal Br. 16).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness. The rejection of claim 5 under 35 U.S.C. § 103(a) as unpatentable over the combination of Thakur '133, Dong, Russell, and Fujita is affirmed. Claims 6–12, 14, and 16–18 are not separately argued and fall with claim 5.

OBVIOUSNESS-TYPE DOUBLE PATENTING:

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness-type double patenting?

FACTUAL FINDINGS (FF)

FF 14. Thakur '308's claim 1 is directed to "[a] method of detecting tumors expressing VPAC receptors in a subject who has, or is suspected of having, such a tumor, said method comprising: (1) administering an effective amount of an imaging compound . . . to the subject; and (2) generating a scintigraphic image of at least part of the subject, wherein . . . [the imaging compound comprises] . . . PACAP, or an analog or fragment thereof which exhibits PACAP biological activity" (Thakur '308 23:21–42; *see* Ans. 7–8).

FF 15. Thakur '308's claim 13 depends from and further limits the tumor of Thakur '308's claim 1 to, *inter alia*, a prostate tumor (Thakur '308 23:66–24:24; Ans. 8).

ANALYSIS

Examiner relies on the combination of Thakur '133, Dong, Russell, and Fujita as discussed above (*see* Ans. 7–8; *see also* FF 1–9). Examiner further finds that the claims of Thakur '308 relate to in vivo "methods of detecting VPAC receptor expressing tumors[, including prostate tumors,] in a subject using labeled PACAP probes" (*see* Ans. 8; *see also* FF 14–15). Thus, based on the combination of claims 1–17 of Thakur '308, in view of Thakur '133, Dong, Russell, and Fujita, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to use Thakur '308's probes to detect tumor cells in a biological sample, in

vitro, as was made obvious by the combination of Thakur '133, Dong, Russell, and Fujita (*see* Ans. 8; *see also id.* at 22).

Thakur '308 discloses PACAP probes that are useful in the detection of tumor cells, including prostate tumors (*see* FF 14–15). Appellant failed to establish an evidentiary basis on this record to support a conclusion that Thakur '308's PACAP probes could not be useful in the in vitro assays suggested by the combination of Thakur '133, Dong, Russell, and Fujita (*see* FF 1–9). Therefore, we are not persuaded by Appellant's contention that Thakur '308 is distinct from the claims on this record because Thakur '308 relates to an in vivo method as opposed to the in vitro assay claimed on this record (Appeal Br. 15–19; Reply Br. 5–6).

For the reasons set forth above, with respect to the obviousness rejection, we are not persuaded by Appellant's contentions regarding the combination of Thakur '133, Dong, Russell, and Fujita (*see* Appeal Br. 18–19; Reply Br. 5–6).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness-type double patenting. The rejection of claim 5 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–17 of Thakur '308, in view of Thakur '133, Dong, Russell, and Fujita is affirmed. Claims 6–12, 14, and 16–18 are not separately argued and fall with claim 5.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
16, 17	112(b)	Indefiniteness	16, 17	
5–12, 14, 16–18	103	Thakur '133, Dong, Russell, Fujita	5–12, 14, 16–18	
5–12, 14, 16–18		Nonstatutory Double Patenting, Thakur '308, Thakur '133, Dong, Russell, Fujita	5–12, 14, 16–18	
Overall Outcome			5–12, 14, 16–18	

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