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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TILMAN LAPPCHEN, HOLGER GRUELL, MARC STEFAN ROBILLARD, and JOHAN LUB

Appeal 2019-004876
Application 14/404,657
Technology Center 1600

Before DONALD E. ADAMS, FRANCISCO C. PRATS, and RACHEL H. TOWNSEND, *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 1–10. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

[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 "Koninklijke Philips N.V." (Appellant's March 8, 2019 Appeal Brief (Appeal Br.) 2).

STATEMENT OF THE CASE

Appellant's disclosure "relates to radiotracers and is described in connection with Positron Emission Tomography (PET) and/or Single Photon Emission Computed Tomography (SPECT) imaging" (Spec.[2] 1: 1–3).

Claims 1, 4, and 5 are representative and reproduced below:

> 1. A method for determining whether compound 0118 is a candidate treatment for a patient, comprising:
>
> processing, via a processor, image data of tissue of interest of the patient administered a radiolabeled analog of compound 0118 and including a cancer to determine whether the radiolabeled analog of compound 0118 is present in the tissue of interest represented in the image data, wherein the radiolabeled analog of compound 0118 includes a radioactive isotope of one of the halogens F, Cl, Br, I, or At; and
>
> generating a signal indicating that compound 0118 is a candidate treatment for the patient in response to the determining that the radiolabeled analog of compound 0118 is present in a predetermined amount in the tissue of interest represented in the image data,
>
> wherein the presence of the radiolabeled analog of compound 0118 in the tissue of interest indicates presence of a sub-type of cancer having a galectin-1 molecular target, which is a sub-type treatable by compound 0118.

(Appeal Br. 6.)

> 4. The method of claim 1, further comprising:
>
> determining the patient has cancer based on image data from an initial scan of the patient which was performed prior to all of the acts of claim 1.

(*Id.*)

> 5. The method of claim 4, wherein the initial scan includes one or more of a [^{18}F]Fluorodeoxyglucose, [^{18}F]fluoride, [^{18}F]

[2] Appellant's December 1, 2014 Specification.

> deoxyfluorothymidine, [^{18}F]fluoromisonidazole, [^{11}C]choline, or [^{11}C]methionine based PET scan.

(*Id.* at 7 (alteration original).)

Grounds of rejection before this Panel for review:

Claims 1–10 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Hsieh,[3] Dings,[4] and Kobus.[5]

Claim 5 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Hsieh, Dings, Kobus, and Weber.[6]

ISSUE

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

FACTUAL FINDINGS (FF)

We adopt Examiner's findings concerning the scope and content of the prior art (*see* Ans.[7] 4–6 and 9) and provide the following findings for emphasis.

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[3] Hsieh et al., US 2009/0123381 A1, published May 14, 2009.
[4] Ruud P.M. Dings et al., *Antitumor Agent Calixarene 0118 Targets Human Galectin-1 as an Allosteric Inhibitor of Carbohydrate Binding*, 55 J. Med. Chem. 5121–29 (2012).
[5] D. Kobus et al., *A fully automated two-step synthesis of an 18F-labelled tyrosine kinase inhibitor for EGFR kinase activity imaging in tumors*, 67 Applied Radiation and Isotopes 1977–84 (2009).
[6] Wolfgang A. Weber, *Technology Insight: novel imaging of molecular targets is an emerging area crucial to the development of targeted drugs*, 5 Nature 44–54 (2008).
[7] Examiner's April 12, 2019 Answer.

FF 1. Compound 0118 (i.e., Calixarene 0118 or Calix[4]arene compound 0118) is an antitumor peptide that targets human galectin-1 (*see generally* Dings Title and Abstract; Spec. 3:27 – 4:4).

FF 2. Examiner finds that the combination of Hsieh and Dings discloses each element of Appellant's claimed method except a "radiolabel[ed] compound 0118" (*see* Ans. 4–5).

FF 3. Examiner finds that Kobus discloses a method of radiolabeling peptides and that Kobus' methodology can be applied to Dings' compound 0118 peptide because "[t]he peptides are labeled on their terminus employing well known chemistry and thus the labeling of the peptides would be highly predictable given this is a standard method of labeling peptides to render them radioactive" (Ans. 8; *see also id.* at 6).

FF 4. Examiner finds:

> Weber discloses that FDG-PET has been used to assess the glycolytic response of tumors to chemotherapy in patients with a wide variety of malignancies. Although the FDG-PET methodology and criteria for tumor responses varied in different studies, changes in FDG uptake by tumors after the first chemotherapy cycle correlate significantly with patient survival in these various studies.

(Ans. 9 (citing Weber 51).)

FF 5. Appellant discloses:

> Although anginex and other anti-angiogenic peptides have shown promising anti-tumor effects *in vivo*, non-peptidic compounds are often superior drugs, mainly because they allow oral administration, generally lack an immune response, and display a better pharmacokinetic profile. Using the 3-dimensional molecular structure of anginex as a template, Dings, et al. "Design of nonpeptidic topomimetics of antiangiogenic proteins with antitumor activities," J Natl Cancer Inst 98(13): 932-936, 2006, designed a small library of

> nonpeptidic, calix[4]arene based surface topomimetics, mimicking the spatial dimensions and the amphipathic nature of key amino acid side chains in anginex. One of these compounds, termed compound 0118, proved equipotent or even more potent than anginex both in *in vitro* assays of endothelial cell proliferation, endothelial cell migration, and angiogenesis, and in tumor growth models *in vivo*. In the meantime, compound 0118 has proven safe in toxicological studies and has already entered clinical studies.
>
> Apart from the promising (pre)-clinical results obtained so far and the high expectations regarding development of compound 0118 into a pharmaceutical for antiangiogenic cancer therapy, radio labelled derivatives of compound 0118 may prove highly valuable PET- and/or SPECT-imaging tracers for tumor diagnosis and/or for selection of patients amenable to treatment with compound 0118. However, such radiolabeled analogues of this compound are unknown. Unfortunately, design of radio labelled analogues of compound 0118 is an intrinsically difficult task given the hitherto known structure activity relationship (SAR) of a range of similar compounds, indicating that only minor modifications are tolerated without a significant loss of anti-angiogenic activity. Moreover, the high molecular weight of this drug molecule compared to other small molecule drugs imposes additional constraints on the design of a related radiotracer, as it is necessary to separate and remove unreacted precursor after radiolabeling in order to obtain a final radiotracer solution of high purity and high specific activity.

(Spec. 3:27 – 4:17.)

ANALYSIS

The rejection over the combination of Hsieh, Dings, and Kobus:

Based on the combination of Hsieh, Dings, and Kobus, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to, *inter alia*, label compound 0118 using Kobus' peptide labeling methodology to produce a radiolabeled analog of compound

0118 for use in a method for determining whether compound 0118 is a candidate treatment for a patient (*see* Ans. 6–7; *see also* FF 1–3).

Appellant contends that "there is no reasonable expectation of success that the combination of Ding and Kobus would result in a radiolabeled analog of compound 0118" because "[w]hen combining prior art references, there must be a reasonable expectation of success and . . . at least some degree of predictability is needed to arrive at a reasonable expectation of success," "[t]he field of chemistry is recognized as a highly unpredictable field," and "[t]he high degree of unpredictability and difficulty pertaining to radiolabeling analogs of compound 0118 is" disclosed in Appellant's Specification (Appeal Br. 3; *see* FF 5; *see also* Reply Br.[8] 2). Thus, Appellant contends

> that due to the high unpredictability in the field of chemistry and the difficulty in creating a radiolabeled analog of compound 0118 one having ordinary skill in the art at the time of the invention would not have had a reasonable expectation of successfully arriving at a radiolabeled analog of compound 0118 by combining Ding and Kobus.

(Appeal Br. 4; *see also* Reply Br. 3.) We are not persuaded.

Initially, we note that "[o]bviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also* Ans. 7 (Examiner makes clear that obviousness requires only a reasonable expectation of success). In this regard, Examiner finds that, notwithstanding Appellant's contention to the contrary, the chemistry required to radiolabel the terminus of a peptide, such as Ding's compound 0118, was well known

[8] Appellant's June 5, 2019 Reply Brief.

in this art at the time of Appellant's claimed invention (*see* Ans. 8 (citing Kobus); *see also* FF 3). As Examiner explains, the evidence on this record establishes that "peptides are labeled on their terminus employing well known chemistry and thus the labeling of [Ding's compound 0118] peptides would be highly predictable given this is a standard method of labeling peptides to render them radioactive" (Ans. 8; *see generally id.* at 8–9). We find no error in Examiner's rationale.

Although, Appellant's Specification discloses that "promising (pre)-clinical results [were] obtained so far" and there were "high expectations regarding development of compound 0118 into a pharmaceutical for anti-angiogenic cancer therapy," we do not find, and Appellant has not identified, a disclosure in Appellant's Specification that supports Appellant's contention that "*the specification directly states* that *the fact that analogs of compound 0118 are anti-angiogenic*, as well as other factors, *make it difficult to radiolabel as other anti-angiogenic compounds tolerate only minor modifications before losing their anti-angiogenic properties*" (Reply Br. 2 (citing Spec. 3:27 – 4:4) (emphasis added); *cf.* FF 5 (reproducing the disclosure of Appellant's Spec. at 3:27 – 4:17).

In addition, we find no argument in Appellant's Appeal Brief related to whether a method of radiolabeling a peptide is dependent upon the activity of the peptide, e.g. whether the peptide is a tyrosine kinase inhibitor or not (*see* Reply Br. 2–3). Therefore, this argument is belated and will not be addressed on the merits. *See Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) (Appellant fails to "explain what 'good cause' there might be to consider the new argument. On this record, Appellant's new argument is belated.").

Furthermore, Appellant's claimed invention does not require compound 0118 to have anti-angiogenic activity and Appellant has not explained why the molecular target (i.e. tyrosine kinase or gla-1) of the peptide would affect its ability to be labeled.

The rejection over the combination of Hsieh, Dings, Kobus, and Weber:

Based on the combination of Hsieh, Dings, Kobus, and Weber, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to include Weber's FDG-PET method in a method for determining whether compound 0118 is a candidate treatment for a patient as suggested by the combination of Hsieh, Dings, and Kobus (*see* Ans. 9; *see also* FF 1–4).

Having found no error in Examiner's conclusion of obviousness based on the combination of Hsieh, Dings, and Kobus, we are not persuaded by Appellant's contention that "Weber does not make up for the above noted deficiencies of Hsieh, Ding and Kobus" (Appeal Br. 5).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness.

The rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Hsieh, Dings, and Kobus is affirmed. Claims 2–10 are not separately argued and fall with claim 1.

The rejection of claim 5 under 35 U.S.C. § 103(a) as unpatentable over the combination of Hsieh, Dings, Kobus, and Weber is affirmed.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–10	103	Hsieh, Dings, Kobus	1–10	
5	103	Hsieh, Dings, Kobus, and Weber	5	
Overall Outcome			1–10	

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