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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte STEVEN NORMAN QUAYLE, SIMON STEWART JONES, KENNETH C. ANDERSON, and TERU HIDESHIMA

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Appeal 2019-002354
Application 14/508,072[1]
Technology Center 1600

_____

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method treating multiple myeloma, which have been rejected as anticipated or obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Lenalidomide and pomalidomide are immunomodulatory (IMiD) drugs that "have demonstrated significant clinical activity in multiple myeloma [("MM")] patients." (Spec. 1.) Appellant's Specification states

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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 Acetylon Pharmaceuticals, Inc. and Dana-Farber Cancer Institute. (Br. 3.)

that "[h]istone deacetylase (HDAC) enzymes represent attractive therapeutic targets in multiple myeloma, but unfortunately non-selective HDAC inhibitors have led to dose-limiting toxicities in patients." (*Id.*) Appellant's invention is directed to combination therapy for MM patients of a histone deacetylase 6 (HDAC6) specific inhibitor and either lenalidomide or pomalidomide.

Claims 50, 52, and 61–65 are on appeal. Claim 1 is representative and reads as follows:

> 50. A method for treating multiple myeloma in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a pharmaceutical combination comprising an HDAC inhibitor having the structure:
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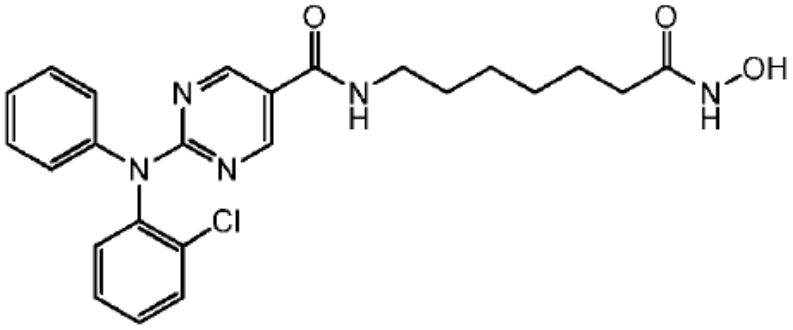
> 
>
> or a pharmaceutically acceptable salt thereof;
>
> and an immunomodulatory drug selected from
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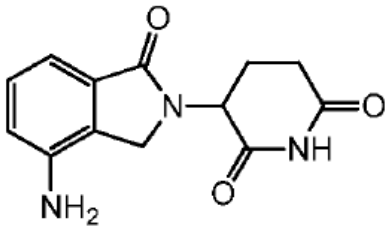
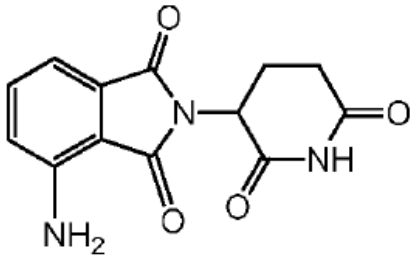
> 
>
> , or a pharmaceutically acceptable salt thereof, and



, or a pharmaceutically acceptable salt thereof.

(Br. 15.)

The following grounds of rejection by the Examiner are before us on review:

Claims 50, 52, 62, 63, and 65 under 35 U.S.C. § 102(a)(2) as anticipated by Raje.[2]

Claim 64 under 35 U.S.C. § 103 as unpatentable over Raje.

Claim 61 under 35 U.S.C. § 103 as unpatentable over Raje and Zeldis.[3]

DISCUSSION

Anticipation

The Examiner finds that Raje teaches a method of treating osteolytic bone lesions associated with multiple myeloma. (Final Action 6.) The Examiner explains that a patient cannot suffer from such bone lesions without also having multiple myeloma. (Ans. 14.)

The Examiner finds that a treatment disclosed by Raje is administration of compound C, the carboxamide depicted below

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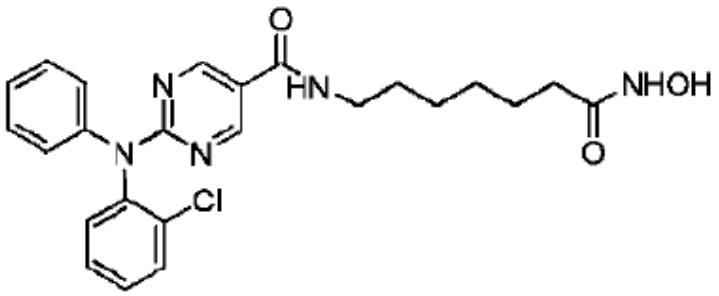
[2] Raje, WO 2013/013113 A2, published Jan. 24, 2013.
[3] Zeldis, US 2008/0317708 A1, published Dec. 25, 2008.



, which is a compound of formula I, in a therapeutically effective amount. (Final Action 6; Ans. 10.) The Examiner explains that compound C of Raje is the claimed compound. (*Id.*)

The Examiner also finds that Raje teaches a method of treating a bone disorder associated with abnormally high bone catabolism, such as primary tumor cell involvement in multiple myeloma. (Final Action 6.) The Examiner explains that Raje teaches the method involves administering a compound of formula I, as well as administering pomalidomide. (*Id.*) The Examiner acknowledges that Raje broadly teaches the use of compounds of formula that are HDAC6 inhibitors for treating bone disorders, but that it "exemplifies Compound C as one of 3 specific embodiments of the disclosed HDAC6 inhibitors of formula (1) . . . for use in treating primary tumor cell involvement in MM . . . and exemplify pomalidomide as one of 4 compounds which can be administered in combination with the HDAC6 inhibitor." (Ans. 10.) In light of the foregoing, the Examiner contends that, even though Raje is silent regarding "treating multiple myeloma" such would be the inevitable result of administering the same claimed compounds to the same claimed "subjects (patients suffering from osteolytic bone lesions associated with multiple myeloma, which are a subset of patients suffering from MM)." (Final Action 7.)

We agree with the Examiner's findings and conclusion of anticipation. Claimed subject matter is anticipated when every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *See Schering Corp. v. Geneva Pharms., Inc.,* 339 F.3d 1373, 1379 (Fed. Cir. 2003). "[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures *not directly related to each other* by the teachings of the cited reference." *In re Arkley,* 455 F.2d 586, 587 (CCPA 1972) (emphasis added). We find the various disclosures relied on by the Examiner to be disclosures that are directly related to each other for the reasons that follow.

Raje discloses "methods for treating disorders associated with excessive bone catabolism (resorption), whether as a result of excessive OCL[4] activity, reduced OBL[5] activity, or both" where the disorder can be "primary tumor cell involvement in multiple myeloma." (Raje 7, 9.) Raje explains that "[m]ultiple myeloma (MM) is a plasma cell malignancy characterized by a high capacity to induce osteolytic bone lesions" and that "70–80% of [MM] patients develop osteolytic bone lesions." (Raje 12.) Thus, we understand Raje to teach that osteolytic bone lesions in MM patients are a result of primary tumor cell involvement in MM.[6]

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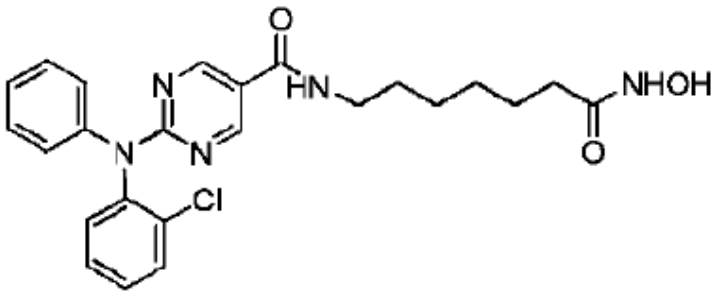
[4] OCL is short for osteoclast. Raje 7.
[5] OBL is short for osteoblast. *Id.*
[6] We note that Raje also describe osteosclerotic lesions can be a result of metastatic bone disease in advanced-stage cancer. (Raje 12.)

Raje further explains that "[t]he methods described herein include the administration of effective amounts of HDAC6-selective inhibitors" that are reverse amide compounds of formula I, such as Compound C. (*Id.* at 14–15, 62.) Compound C is the claimed compound depicted below.



Raje teaches in particular: "In another embodiment, provided herein is a method of treating osteolytic bone lesions associated with MM in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound C." (*Id.* at 62.) Raje also teaches combination therapy "to improve treatment efficacy" "for the treatment or reducing risk of" bone lesions associated with MM with a reverse amide HDAC6 inhibitor of formula I where the additional active agent may be pomalidomide or lenalidomide. (*Id.* at 65–66.) While Raje specifically points to Compound A (*id.*) as one particular example of an HDAC6 inhibitor of formula I for such use, we do not find that disclosure to be one that excludes the other formula I compounds described. That is because Raje states that the combination therapy in which "the administration of additional active agents to improve treatment efficacy" is in combination with "a reverse amide HDAC6 inhibitor as described herein." (*Id.*) And as discussed above, Compound C is specifically identified as a reverse amide

HDAC6 inhibitor to administer for treating osteolytic bone lesions associated with MM. (*Id.* at 62.)

Furthermore, while Raje indicates pomalidomide and lenalidomide as active agents for combination therapy in a list of nine active agents, we conclude that the disclosure is sufficient for anticipation. *Perricone v. Medicis Pharmaceutical Corporation*, 432 F.3d 1368 (Fed. Cir. 2005) ("In total, Pereira teaches a total of fourteen skin benefit ingredients. This court rejects the notion that one of these ingredients cannot anticipate because it appears without special emphasis in a longer list.")

For the foregoing reasons, we disagree with Appellant that Raje "does not clearly and unequivocally disclose the claimed method" (Br. 6–9).

Appellant further argues that "the Examiner has not properly established that the method of treating bone disease disclosed in Raje could necessarily be effective for treating the general disease of multiple myeloma in a subject in need thereof." (*Id.* at 9–10.) We do not find this argument persuasive. As discussed above, and articulated by the Examiner, Raje discloses combination therapy for treating osteolytic bone lesions associated with MM. We agree with the Examiner that a patient with osteolytic bone lesions associated with MM necessarily has MM. (Ans. 14.) Appellant does not dispute the foregoing. Furthermore, in treating the bone lesions induced by MM, the therapy with Compound C would necessarily treat an element of MM in the patient, namely the MM induced bone lesions. Moreover, Raje discloses that known MM therapies include use of immunomodulatory drugs, and lenalidomide and pomalidomide are immunomodulatory drugs that Raje discloses to use in conjunction with a reverse amide HDAC6 inhibitor (Raje 65) described for treating with osteolytic bone lesions

associated with MM, such as Compound C (Raje 62). Consequently, the combination therapy taught by Raje that includes administration of pomalidomide would inherently treat MM. We agree with the Examiner, that whether or not specifically identified by Raje, the treatment method disclosed for treating patients with osteolytic bone lesions associated with MM, a subset of patients with MM, would necessarily result in treating MM via both the immunomodulatory drug which is known to treat MM, as well as Compound C which is described to treat osteolytic bone lesions that are a result of MM, because the patient population is the same as the claimed population. (Ans. 14–15); *Cf. Perricone*, 432 F.3d 1376–79 (finding claims directed to a method for treating skin sunburn comprising topically applying to the skin sunburn not to be anticipated by a prior art reference that taught a cosmetic composition for topical application to skin because "[s]kin sunburn is not analogous to skin surfaces generally" and the prior art reference "does not disclose topical application to skin sunburn," and "is silent about any sunburn prevention or treatment benefits").)

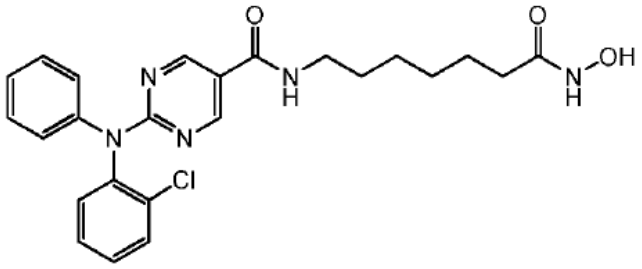
Thus, for the foregoing reasons, we affirm the Examiner's rejection of claim 50 as being anticipated by Raje.

Claims 52, 62, 63, and 65 have not been argued separately and therefore fall with claim 50. 37 C.F.R. § 41.37(c)(1)(iv).

II

Obviousness of claim 64

Claim 50 requires administration of "a pharmaceutical combination" comprising the HDAC inhibitor having the following structure



and one of either lenalidomide or pomalidomide. Claim 64 requires that the HDAC inhibitor and IMiD drug of the pharmaceutical combination are administered at different times.

Claim 64 depends from claim 50 and further recites "wherein the HDAC inhibitor and the immunomodulatory drug are administered at different times." The Examiner notes that Raje does not specifically teach administering the HDAC inhibitor and the immunomodulatory drug at different times in the method of treating osteolytic bone lesions associated with MM in a subject in need thereof. (Final Action 14.) However, the Examiner finds that Raje does "teach in some embodiments, these additional agents [i.e., the second agent in the combination therapy,] can be administered substantially concurrently with (e.g. in separate or the same dose form) or can be administered concurrently." (*Id.*) Thus, the Examiner finds that it would have been obvious to one of ordinary skill in the art with a reasonable expectation of success to carry out the combination therapy treating osteolytic bone lesions associated with MM taught by Raje by administering separate dose forms at different times based on the therapeutic needs of the patient. (*Id.*)

We agree with the Examiner's findings and conclusion of obviousness.

Raje states, when describing combination therapies, such as "for the treatment or reducing risk of a condition described herein, e.g., bone loss, e.g., bone lesions associated with multiple myeloma". . . "[i]n some embodiments, these additional agents can be administered substantially concurrently with (e.g., in separate or the same dose form) or can be administered concurrently." (Spec. 65–66.) In other words, Raje does not indicate that combination therapy is only effective with administration of the active agents at the same time and in the same dose form. Rather, the therapy can involve administering separate dose forms of the drugs "substantially" concurrently with, i.e., each therapeutic does not have to be administered at the same time. Thus, we agree with the Examiner that it would have been obvious to one of ordinary skill in the art to administer compound C and pomalidomide in combination therapy to treat bone lesions associated with MM at different times with a reasonable expectation of success.

Appellant argues that "Raje provides no motivation to one of skill in the art to arrive at the combinations specified in instant claim 50" and thus concludes that claim 64 is also not obvious. (Br. 10.) As noted above, we agree with the Examiner that Raje anticipates claim 50. Thus, we do not find this argument as to the non-obviousness of claim 50, and the consequent non-obviousness of claim 64, persuasive.

Appellant further argues that "the claimed methods embody unexpected results." (*Id.*) It is well established that evidence of unexpected results may not overcome a rejection based on anticipation. *See, e.g.*, *In re Malagari*, 499 F.2d 1297, 1302 (CCPA 1974) ("If the rejection under § 102 is proper . . . appellant cannot overcome it by showing such unexpected

results or teaching away in the art, which are relevant only to an obviousness rejection."). Thus, Appellant's argument as it pertains to claim 50, which is anticipated by Raje, is not persuasive.

Moreover, as to claim 64, "[i]t is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims." *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972); *In re Peterson*, 315 F.3d 1325, 1330–31 (Fed. Cir. 2003). Claim 64 requires the HDAC inhibitor and the immunomodulatory drug to be administered at different times. As the Examiner explains, the evidence relied upon by Appellant (Br. 11 (pointing to Example 14 of the Specification)), does not indicate that the claimed HDAC and the immunomodulatory drug are administered at different times. Thus, the evidence Appellant points to for unexpected results is not commensurate in scope with claim 64 and is not persuasive of nonobviousness.

Therefore, for the foregoing reasons, we affirm the Examiner's rejection of claim 64 as being obvious over Raje.

Obviousness of claim 61

Claim 61 depends from claim 50, and further recites "the subject was previously refractory to an immunomodulatory drug." The Examiner finds that Zeldis teaches a method of treating MM comprising administering pomalidomide and a therapeutically effective amount of a second agent to a patient that is refractory to conventional therapy including refractory to an immunomodulatory drug. (Final Action 14–15, 17.) The Examiner explains that "Zeldis teaches the cancer is refractory or resistant to chemotherapy or radiation; in particular refractory to thalidomide [0102]." (*Id.* at 17; Ans.

19.) The Examiner notes that "[t]halidomide reads on an immunomodulatory drug as evidenced by the instant [S]pecification which teaches the IMiD is preferably thalidomide (see page 25, lines 10-12)." (*Id.*) The Examiner concludes that in light of Zeldis' teachings, it would have been obvious to one of ordinary skill in the art with a reasonable expectation of success to use the treatment of Raje, i.e., administration of compound C and pomalidomide to treat a bone disorder associated with primary tumor involvement in MM in a subject in need thereof, where the MM is refractory to an immunomodulatory drug. (Final Action 15, 17; Ans. 19.)

Appellant argues that Zeldis teaches immunomodulatory agents for the treatment of MM which is relapsed, refractory, or resistant to conventional therapy, where conventional therapies are described as "'surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy, and immunotherapy' and other non-drug type therapies." (Br. 12.) Thus, argues Appellant, "Zeldis teaches treatment of cancers that are refractive to conventional therapies using immunomodulatory agents, and does not teach treatment of cancers that are refractory to immunomodulatory agents as specified in the instant claims" and the reference does not render obvious claim 61. (*Id.* at 13.) We do not find Appellant's argument persuasive.

We agree with the Examiner that Zeldis teaches MM treatment using pomalidomide where the cancer is refractory to thalidomide, an immunomodulatory drug. There is no dispute that thalidomide is an immunomodulatory drug. (*See* Spec. 25:19–20.) Zeldis states:

> In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation; in particular, refractory to thalidomide.

(Zeldis ¶ 102.) In short, Zeldis equates treatment with thalidomide to "chemotherapy or radiation." And, Zeldis teaches these treatments are examples of therapies conventionally used to treat, prevent or manage cancer. (*Id.* ¶ 18.)

Thus, not only does Zeldis teach treating cancer that is refractory to prior treatment with an immunomodulatory agent (Br. 12), it also explicitly teaches, as the Examiner pointed out in the Answer to which Appellant does not respond, that the cancer to be so treated may be refractory to thalidomide, an undisputedly immunomodulatory agent (Ans. 19).

Thus, for the foregoing reasons, we affirm the Examiner's rejection of claim 61 as being obvious over Raje and Zeldis.

SUMMARY

In summary:

Claims Rejected	Basis	Affirmed	Reversed
50, 52, 62, 63, 65	§ 102(a)(2) Raje	50, 52, 62, 63, 65	
64	§ 103 Raje	64	
61	§ 103 Raje and Zeldis	61	
Overall Outcome		50, 52, and 61–65	

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