

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte

MARTIN BURKE, MARIA-CHRISTINA WHITE, MARK C. WATTS,
JAE KYOO LEE, BETTY M. TYLER, GARY H. POSNER,
and HENRY BREM

Appeal 2008-2118¹
Application 10/223,685
Technology Center 1600

Decided: June 26, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and LORA M. GREEN,
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 11-17, all of the claims remaining in the application. The claims

¹ Heard June 10, 2008.

stand rejected as unpatentable over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

The present invention is directed to localized delivery of vitamin D₃ or a vitamin D₃ analog directly to a tumor site using a biodegradable controlled release polymeric matrix.

Claims 11-17 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Bishop (U.S. Patent 5,795,882, issued August 18, 1998) in view of Brem (U.S. Patent 5,626,862, issued May 6, 1997).²

Appellants have not argued the rejected claims separately.³ Therefore, we select claim 11 as representative of the claimed subject matter for the purpose of deciding this appeal, and claims 12-17 will stand or fall with claim 11. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 11 reads as follows:

11. A method of treating a patient to inhibit tumor viability or proliferation comprising locally administering to the patient at a site where tumor is found a controlled or sustained release formulation comprising vitamin D₃ or vitamin D₃ analog having antiproliferative activity, and a biodegradable polymeric matrix; wherein the formulation is administered in an amount to inhibit tumor viability or proliferation.

² A rejection of claim 13 under 35 U.S.C. § 112, second paragraph was withdrawn by the Examiner (Ans. 2-3).

³ In this decision we consider only those arguments actually made by Appellants in the Briefs. Arguments that Appellants could have made but chose not to make in the Briefs have not been considered and are deemed to have been waived. See 37 C.F.R. § 41.37(c)(1)(vii).

FINDINGS OF FACT (FF)

The Claimed Invention

1. Claim 11 on appeal is directed to a method of treating a patient to inhibit tumor viability or proliferation by locally administering a controlled or sustained release formulation comprising a biodegradable polymeric matrix and an effective amount of vitamin D₃ or a vitamin D₃ analog having antiproliferative activity, at a site where a tumor is found.

2. None of the claims on appeal is limited to treating tumors located at any particular site in the body, or to treating any particular type of tumor.

Bishop

3. Bishop teaches that “[a]ntiproliferative and differentiating actions of 1 α ,25-dihydroxyvitamin D₃ and other vitamin D₃ analogues have been reported with respect to prostate cancer cell lines” (Bishop, col. 3, ll. 3-5), however, “their practical use in differentiation therapy as anticancer agents is severely limited because of their equally high potency as agents affecting calcium metabolism” (Bishop, col. 3, ll. 13-16), that is, their propensity to induce hypercalcemia - “unphysiologically high and deleterious blood calcium levels” (Bishop, col. 6, ll. 41-42).

4. Bishop describes a “treatment for a patient suffering from a hyperproliferative disease such as prostatic cancer . . . which includes administering a medicament that is 1 α -hydroxyprevitamin D or a DSR [delayed sustained release] active vitamin D or active previtamin D . . . without [the] dose-limiting hypercalcemia” (Bishop, col. 6, ll. 35-42) “observed after the same amount of activated vitamin D is administered in previously known [oral] formulations” (Bishop, col. 6, ll. 52-54).

5. Bishop uses two basic strategies for providing antiproliferative effective levels of vitamin D₃ in a patient's blood stream, while avoiding dose-limiting hypercalcemia (i.e., dose-limiting toxicity) "associated with other oral dosing of vitamin D forms" (Bishop, Abstract). Essentially, the first strategy is to administer a formulation comprising a previtamin D in a sustained release matrix, so that the previtamin is not converted to the active vitamin D compound until after it is absorbed through the intestine and thus, does not stimulate vitamin D receptors in the intestine that trigger calcium uptake from the intestine. The second strategy is to bypass the receptors in the intestine altogether, by administering the previtamin or the active vitamin in a delayed, sustained release matrix, ensuring that most of the previtamin or the active vitamin is absorbed at a point beyond the proximal portion of the small intestine (Bishop, col. 4, l. 28 to col. 5, l. 34).

6. Bishop teaches that "the pharmacologically active compounds . . . can be employed in admixtures . . . suitable for enteral (e.g., oral) or parenteral application" (Bishop, col. 13, ll. 55-64), but "the preferred route of administration is oral" (Bishop, col. 3, l. 55).

7. Enteral and parenteral administration are both systemic methods of administration.

Brem

8. Brem describes "a chemotherapeutic composition and method of use thereof which provides for effective long term release of chemotherapeutic agents that are not stable or soluble in aqueous solutions or which have limited bioavailability in vivo for treatment of solid tumors" and which "avoids high systemic levels of the agent and associated toxicities" (Brem, col. 3, ll. 40-48).

9. Brem teaches that “[d]elivering chemotherapeutic drugs locally to a tumor is an effective method of prolonging tumor exposure to the drug while minimizing the drug’s dose-limiting systemic side effects” (Brem, col. 4, ll. 47-50).

10. Brem describes “devices consist[ing] of reservoirs which release drug over an extended time period while at the same time preserving the bioactivity and bioavailability of the agent” (Brem, col. 3, ll. 55-57). The devices consist of “biodegradable polymeric matrixes . . . [which] are implanted within or immediately adjacent the tumors to be treated” (Brem, col. 3, ll. 58-63).

11. “In general, the effective dosage of a chemotherapeutic agent which is administered locally by extended release will be significantly less than the dosage for the same drug administered for shorter periods of time” (Brem, col. 7, ll. 36-40). “Dosages must be optimized depending on the size of the implant, the location and size of the tumor to be treated, and the period over which drug is to be delivered. These calculations are routine for those skilled in the art of administering chemotherapy to tumor patients” (Brem, col. 7, ll. 32-36).

12. Brem’s “preferred chemotherapeutic agents are camptothecin and paclitaxel, which are insoluble in water, relatively insoluble in lipid . . . , high molecular weight (i.e., of a molecular weight not normally crossing the blood brain barrier), exhibit rapid non-renal clearance in vivo, and have substantial systemic toxicity” (Brem, col. 7, ll. 20-24).

Additional Findings

13. The Examiner finds that vitamin D₃ and many vitamin D₃ analogs are insoluble in water (Ans. 8-9).

DISCUSSION

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that “the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). “Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed” (*id.* at 1740-41). To paraphrase *KSR*, if a technique has been used to improve one process, and a person of ordinary skill in the art would recognize that it would improve similar processes in the same way, using the technique is obvious unless its actual application is beyond his or her skill (*id.* at 1740).

The Examiner contends that it would have been obvious, and one of ordinary skill in the art would have been motivated, “to administer locally at the tumor site a controlled or sustained release formulation comprising a vitamin D3 analog in a biodegradable polymer matrix . . . [to] avoid[] high systemic levels of vitamin D3, [and] associated toxicities” (Ans. 5).

Appellants contend essentially that one of skill in the art would have had no reason to administer vitamin D₃ or its analogs locally, and would not, in any case, have had a reasonable expectation of success in inhibiting tumor viability or proliferation by doing so.

The issue raised by this appeal, then, is whether administering vitamin D₃ or a vitamin D₃ analog locally, at the site of a tumor, would have been obvious at the time of the invention, given the scope and content of the prior art, the level of ordinary skill in the art, and the differences between the claimed invention and the prior art.

We agree with the Examiner's conclusion that the claimed invention is unpatentable over the prior art, given the recognition in the art that vitamin D₃'s propensity to induce hypercalcemia limits its practical use as an anti-cancer, anti-proliferative agent in treating prostate cancer (FF 3), and the recognition in the art that delivering a chemotherapeutic agent to a tumor locally in a biodegradable extended release matrix is an effective method of prolonging tumor exposure to the agent while minimizing its dose-limiting systemic side-effects (FF 8, 9). We are not persuaded otherwise by Appellants' arguments.

Specifically, we are not persuaded by Appellants' argument that “[l]ocal administration is the opposite of systemic administration” (App. Br. 13), thus, administering vitamin D₃ locally would “change the principle of operation of Bishop” (App. Br. 12-13). The Examiner has established that Vitamin D₃ was known as an anti-tumor agent subject to dose-limiting systemic side effects (FF 3). While Bishop used two particular strategies to avoid vitamin D₃'s systemic side effects in treating prostate cancer (FF 4, 5),

the Examiner has established that local administration of an anti-tumor agent was also known to be an effective strategy for prolonging exposure of a solid tumor to the agent while minimizing the agent's dose-limiting systemic side-effects (FF 9). In our view, the evidence relied on by the Examiner is sufficient to establish that one of skill in the art would have had reason to treat prostate cancer by local, extended release of vitamin D₃ or its analogs to the site of a prostate tumor.

Nor are we persuaded by Appellants' assertion that Bishop teaches away from administering vitamin D₃ locally since Bishop "repeatedly discloses that a threshold vitamin D₃ blood level is necessary to achieve the antiproliferative effects of vitamin D₃ (App. Br. 13), and that "oral [i.e., systemic] dosing of vitamin D₃ and vitamin D₃ analogs can achieve this threshold blood level" (App. Br. 13). If we understand Appellants' implication, it is that Bishop teaches that vitamin D₃ is only effective as an antiproliferative agent if threshold systemic blood levels are achieved. That is not what Bishop teaches. Bishop merely teaches that prior art oral formulations of vitamin D₃ (prior art to Bishop, that is) were capable of achieving antiproliferative blood levels, but were associated with unacceptable systemic side effects, while comparable antiproliferative levels could be achieved, without the unacceptable side effects, using Bishop's sustained release formulations (FF 4). Again, local administration of an anti-tumor agent was known in the art as an alternative effective strategy for minimizing the agent's dose-limiting systemic side-effects (FF 9), and we

see nothing in Bishop that suggests that that strategy would be unproductive with vitamin D₃ or its analogs.

Appellants also contend that Brem teaches local administration of unrelated “chemotherapeutic agents [that] do not cross the blood brain barrier and are characterized by poor bioavailability” (App. Br. 12), while “[v]itamin D₃ does not exhibit low bioavailability” (App. Br. 12). Again, this argument is not persuasive. Brem’s disclosure is not as narrow as characterized by Appellants. Again, Brem teaches that local administration of an anti-tumor agent (especially one that is unstable or insoluble in aqueous solution) in a biodegradable controlled release matrix is one way of maximizing a solid tumor’s exposure to the agent, while minimizing its dose-limiting systemic side effects (FF 8, 9). Bishop teaches that vitamin D₃ (which the Examiner finds is insoluble in water (FF 13)) is an effective anti-tumor agent, but exhibits dose-limiting systemic side effects, e.g., hypercalcemia (FF 3).

Finally, we are not persuaded by Appellants’ argument that Brem teaches that “the predictability of the efficacy of chemotherapeutic agents remains low . . . drugs that are effective systemically may not be effective when administered locally” (Brem, col. 2, ll. 39-45; App. Br. 14). Brem does not further elaborate, and the statement is so generic we do not agree with Appellants that it would “discourage[] one of ordinary skill in the art from modifying the teachings of Bishop” (App. Br. 14), especially as Brem also teaches that local administration is an effective way of exposing a solid tumor to effective amounts of an anti-tumor agent while minimizing systemic side effects (FF 9).

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We conclude that the Examiner has properly applied the *Graham* factors and the cited references provide a reason to combine their teachings, as well as a reasonable expectation of success. Accordingly, the rejection of claims 11-17 under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv) (2006).

AFFIRMED

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