

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte DARRELL H. CARNEY, ROGER S. CROWTHER,
JANET STIERNBERG, and JOHN BERGMANN

Appeal 2008-4806
Application 10/999,223
Technology Center 1600

Decided: January 12, 2009

Before ERIC GRIMES, RICHARD M. LEOVITZ, and MELAINE L.
McCOLLUM, *Administrative Patent Judges*.

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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a cartilage growth or repair stimulation method. The Examiner has rejected the claims as not being enabled and as not being supported by an adequate written description. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Claims 1-10, 13-16, and 21-24 are on appeal. Claims 11, 12, and 17-20 are also pending but have been withdrawn from consideration by the Examiner.

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). We will focus on claim 1, the broadest claim on appeal, which reads as follows:

1. A method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair, said method comprising administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor.

Claims 1-10, 13-16, and 21-24 stand rejected under 35 U.S.C. § 112, first paragraph:

“as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention” (Ans. 3), and

“because the specification, while being enabling for the agonist set forth in SEQ ID NO: 6, . . . does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims” (Ans. 6).

ISSUES

Did the Examiner err in concluding that the Specification does not provide written description support for or enable the full scope of “an agonist of the non-proteolytically activated thrombin receptor,” as recited in claim 1?

FINDINGS OF FACT

1. Non-proteolytically activated thrombin receptor (hereinafter “NPAR”) is “a high-affinity thrombin receptor present on the surface of most cells” (Spec. 4: 2-16).

2. “NPAR appears to mediate a number of cellular signals that are initiated by thrombin independent of its proteolytic activity. . . . NPAR is therefore characterized by its high affinity interaction with thrombin at cell surfaces and its activation by proteolytically inactive derivatives of thrombin and thrombin derived peptide agonists.” (*Id.* at 4: 20-26.)

3. “Compounds which stimulate or activate NPAR are said to be NPAR agonists” (*id.* at 4: 15).

4. “NPAR agonists and antagonists can compete for the affinity binding with thrombin to cells” (*id.* at 4: 18-19).

5. TP508, “a fragment of human thrombin corresponding to prothrombin amino acids 508-530 (SEQ ID NO: 5),” is an NPAR agonist (*id.* at 2: 13-14, 5: 29 to 6: 1, & 7: 26-27).

6. The Specification states that “NPAR agonists can induce cartilage growth and repair when administered to sites needing cartilage growth and/or repair” (*id.* at 4: 12-14).

7. The Specification also states that “NPAR activation can be assayed based on the ability of its agonists to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C as disclosed in U.S.

Patent Nos. 5,352,664¹ and 5,500,412²” (collectively referred to herein as the “Carney patents”) (*id.* at 4: 26-29).

8. In addition, the Specification states that “[o]ne example of an NPAR agonist is a thrombin peptide derivative and physiologically functional equivalents, i.e., a polypeptide with no more than about fifty amino acids, preferably no more than about thirty amino acids and having sufficient homology to the fragment of human thrombin corresponding to prothrombin amino acids 508-530 (SEQ ID NO: 5) that the polypeptide activates NPAR” (*id.* at 5: 26 to 6: 1).

9. The Specification also states that a “physiologically functional equivalent of a thrombin derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence” (*id.* at 6: 12-15).

10. The Specification defines a “thrombin receptor binding domain” as “a polypeptide which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha thrombin” (*id.* at 6: 20-22).

11. “Serine esterases, e.g., trypsin, thrombin, chymotrypsin and the like, have a region that is highly conserved” (*id.* at 6: 7-8). The Specification states that “‘Serine esterase conserved domain’ refers to a polypeptide having the amino acid sequence of one of these conserved regions or is sufficiently homologous to one of these conserved regions such

¹ Carney et al., U.S. Patent No. 5,352,664, Oct. 4, 1994 (“Carney 1994”).

² Carney et al., U.S. Patent No. 5,500,412, Mar. 19, 1996 (“Carney 1996”).

that the thrombin peptide derivative retains NPAR activating ability” (*id.* at 6: 8-11).

12. The Specification discloses a “serine esterase conserved sequence ha[ving] the amino acid sequence of SEQ ID NO: 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val) or a C-terminal truncated fragment of a polypeptide having the amino acid sequence of SEQ ID NO: 1” (*id.* at 6: 23-26).

13. The Specification also discloses a “serine esterase conserved sequence ha[ving] the amino acid sequence of SEQ ID NO: 2 (Cys-X₁-Gly-Asp-Ser-Gly-Gly-Pro-X₂-Val; X₁ is Glu or Gln and X₂ is Phe, Met, Leu, His or Val) or a C-terminal truncated fragment thereof” (*id.* at 7: 6-9).

14. The Specification states that “TP508 is an example of a thrombin peptide derivative and has the amino acid sequence of SEQ ID NO: 5” and that a “physiologically functional equivalent of SEQ ID NO: 5 is SEQ ID NO: 6 which has the identical amino sequence of SEQ ID NO: 5 and also contains a C-terminal amide” (*id.* at 7: 26-29).

15. The Specification also states that “[o]ther NPAR agonists include small organic molecules which bind and activate NPAR” and that

[a]gonists of this type can be conveniently identified with high through-put screening, e.g., with assays that assess the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C or with assays that assess the ability of these molecules to compete with

¹²⁵I-thrombin to cells with surface NPAR receptors, as disclosed in Glenn³ . . . [and the Carney patents,] the disclosures of which have been incorporated into the Specification by reference (*id.* at 9: 6-13).

16. In addition, the Specification states that the “term ‘NPAR agonist’ also includes compounds and combinations of compounds known to activate NPAR” and that “[e]xamples are disclosed in [the Carney patents] and include thrombin and DIP-alpha-thrombin” (*id.* at 9: 14-16).

17. Glenn discloses: “Initiation of cell proliferation by thrombin requires signals generated by thrombin interaction with specific high-affinity receptors and thrombin enzymatic activity. Using synthetic peptides representing various domains of thrombin, we have identified a region adjacent to the proteolytic pocket of thrombin which confers high-affinity binding and generation of mitogenic signals.” (Glenn, Abstract (parenthetical omitted)).

18. In particular, Glenn discloses that “[o]ne peptide, representing residues 508 to 530 of human prothrombin (p508-530), . . . enhances the ability of thrombin to stimulate DNA synthesis and stimulates DNA synthesis in cells treated with 25 ng/ml phorbol myristate acetate (PMA). Thus, this peptide or a portion of this peptide appears to represent the high-affinity receptor binding domain of thrombin.” (*Id.*)

19. Glenn also discloses that, “[i]n contrast to the 23 amino acid peptide (p508-530), the tetrapeptide RGDA (p517-520) contained in this

³ Kevin C. Glenn et al., *Synthetic Peptides Bind to High-Affinity Thrombin Receptors and Modulate Thrombin Mitogenesis*, 1 PEPTIDE RESEARCH 65 (1988).

region competes for ¹²⁵I-thrombin binding . . . , but inhibits rather than simulates the mitogenic effects of α -thrombin” (*id.*).

20. Thus, Glenn discloses:

peptides representing portions of the binding domain of thrombin: i) can generate receptor-occupancy related signals that enhance thrombin mitogenesis and are themselves mitogenic in cells treated with PMA; or ii) in the case of RGDA (which may be too small to generate signals), can act as antagonists, inhibiting the mitogenic effects of thrombin by preventing thrombin-receptor interaction.

(*Id.*)

21. The Carney patents each states that “one may formulate polypeptide thrombin derivatives, or their physiologically functional equivalents, which selectively inhibit the interaction of thrombin with its high-affinity receptor or which mimic the stimulatory effects of thrombin” (Carney 1994, col. 3, ll. 26-31; Carney 1996, col. 3, ll. 17-21).

22. Thus, the Carney patents each states that it “relates to synthetic or naturally derived polypeptide agonists and antagonists of thrombin receptor mediated events” (Carney 1994, col. 3, ll. 32-35; Carney 1996, col. 3, ll. 22-25).

23. Each of the Carney patents also states that both agonists and antagonists “possess a thrombin receptor binding domain which includes a segment of the polypeptide that is capable of selectively binding to the high-affinity thrombin receptor. This segment of the polypeptide includes a sequence of amino acids homologous to a tripeptide cell binding domain of fibronectin.” (Carney 1994, col. 3, ll. 35-41; Carney 1996, col. 3, ll. 25-30.)

24. However, the Carney patents each states that “the stimulatory (agonistic) polypeptides [also] possess a sequence of amino acids having sequences derived from the N-terminal amino acids of a dodecapeptide previously shown to be highly conserved among serine proteases,” but that “the inhibitory polypeptides do not include these serine esterase-conserved sequences” (Carney 1994, col. 3, ll. 42-48; Carney 1996, col. 3, ll. 31-38).

WRITTEN DESCRIPTION

Principles of Law

The first paragraph of 35 U.S.C. § 112 “requires a ‘written description of the invention’ which is separate and distinct from the enablement requirement.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). An adequate written description of a chemical invention “requires a precise definition, such as by structure, formula, chemical name, or physical properties.” *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). “A description of what a material does, rather than of what it is, usually does not suffice.” *Rochester*, 358 F.3d at 923; *Eli Lilly*, 119 F.3d at 1568. Instead, the “disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.” *Id.* However, not all functional descriptions “necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003).

In addition, possession of a genus “may be achieved by means of a recitation of a representative number of [compounds] . . . falling within the scope of the genus.” *Eli Lilly*, 119 F.3d at 1569. “Possession may not be shown by merely describing how to obtain possession of members of the claimed genus.” *Ex parte Kubin*, 83 USPQ2d 1410, 1417 (BPAI 2007) (citing *Rochester*, 358 F.3d at 927).

Analysis

The Examiner finds that the “claims are drawn to a broad variable genus of any agonist of NPAR” (Ans. 10). The Examiner finds that Appellants “have described TP508 an agonist of NPAR, however, that species is not representative of the entire genus recited in the claims” (*id.* at 11). In particular, the Examiner finds that “as indicated by the specification NPAR agonist[s] . . . include small organic molecules which bind and activate NPAR” (*id.* at 12). The Examiner concludes that the “skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agonists of NPAR” (*id.* at 12-13).

We agree with the Examiner. As noted by the Examiner, the Specification states that the “NPAR agonists include small organic molecules which bind and activate NPAR” (Finding of Fact (FF) 15). The Specification also states:

Agonists of this type can be conveniently identified with high through-put screening, e.g., with assays that assess the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C or with assays that assess the ability of these molecules to compete with ¹²⁵I-thrombin to cells with surface NPAR receptors.

(FF 15.) However, the Specification does not describe any non-peptide small organic molecules that bind and activate NPAR, nor does the Specification disclose the physical properties or provide another precise definition of these molecules. Therefore, we conclude that the Specification does not adequately describe species representative of the genus of NPAR agonists recited in claim 1.

Appellants contend that they “have recognized that a class of molecules structurally related to a portion of thrombin, bind to a receptor distinct from those receptors previously recognized as activated by protease activity” and that the “so-called NPAR agonists have the common property of binding to the non-proteolytically activated thrombin receptor, and thus have the common structural feature of fitting into the receptor binding site” (App. Br. 3). Appellants also contend that “NPAR agonists are described in the specification as comprising a thrombin receptor binding domain and a serine esterase conserved sequence” and that “[e]xamples of the amino acid sequences of serine esterase conserved sequences are given” (*id.* at 3-4). Thus, Appellants argue that it “can be clearly recognized from the specification that the inventors had this inventive concept” (*id.* at 4).

We are not persuaded. Assuming that all of the claimed compounds have “the common structural feature of fitting into the receptor binding site,” not all compounds that fit into the NPAR binding site will be NPAR agonists (FF 4, 9-11, 19-20, & 23-24). Thus, Appellants have not shown that the structural feature of fitting into the receptor binding site is “sufficiently correlated to” the function of stimulating or activating NPAR to describe NPAR agonists generally.

In addition, claim 1 does not require that the NPAR agonists include a thrombin receptor binding domain and a serine esterase conserved sequence. Instead, the Specification broadly defines NPAR agonists as “[c]ompounds which stimulate or activate NPAR” (FF 3). In addition, the Specification specifically indicates that “NPAR agonists include small organic molecules which bind and activate NPAR” (FF 15). Thus, the disclosure of amino acid sequences of serine esterase conserved sequences is not representative of the genus of NPAR agonists recited in claim 1.

Conclusion of Law

Appellants have not rebutted the Examiner’s prima facie case that the Specification does not adequately describe species representative of the genus of NPAR agonists recited in claim 1. We therefore affirm the written description rejection of claim 1. Claims 2-10, 13-16, and 21-24 fall with claim 1.

ENABLEMENT

Principles of Law

“[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). “It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.” *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). In addition, “sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention . . . means that the disclosure must adequately guide the art worker to determine, without undue

experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.” *Id.*

Analysis

The Examiner finds that the “claimed invention is directed to a method, which encompasses a large genus of agonists, which are highly variable,” and that “[u]ndue experimentation would be required for a skilled artisan to make and test all the possible variants/fragments encompassed in the claims” (Ans. 6-7). In particular, the Examiner notes that the Specification indicates that “NPAR agonists can be small organic molecules that bind and activate NPAR” (*id.* at 13).

Small organic molecules as recognized by the art can include for example, proteins, nucleic acids, carbohydrates, antibodies, lipids, metal ions, cell organelles, cells, ions, viruses, metals, to name a few. Therefore, a skilled artisan has to make and test all possible compounds for example nucleic acids to determine if they bind and activate NPAR to be considered to be a NPAR agonist, then move to the next grouping, for example the proteins and so on.

(*Id.* at 13-14.) Thus, the Examiner finds that “the claimed invention is a starting point and is inviting one skilled in the art to engage in undue experimentation absent sufficient guidance” (*id.* at 13).

We agree with the Examiner. As noted above, the Specification states that the “NPAR agonists include small organic molecules which bind and activate NPAR” (FF 15). The Specification also states:

Agonists of this type can be conveniently identified with high through-put screening, e.g., with assays that assess the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C or with

assays that assess the ability of these molecules to compete with ¹²⁵I-thrombin to cells with surface NPAR receptors.

(FF 15.) However, the Specification does not provide sufficient guidance as to which non-peptide small organic molecules should be subjected to these assays in order to identify NPAR agonists. Therefore, we agree that it would require undue experimentation to make and use NPAR agonists within the full scope of claim 1.

Appellants contend that “it is routine in the art to perform screening assays in which a large number of peptides of different amino acid sequences are tested for their binding properties or their ability to stimulate proliferation of fibroblasts” (App. Br. 4). In particular, Appellants refer to the Specification at “page 9, lines 5-13, wherein it is described that agonists of the non-proteolytically activated thrombin receptor (‘NPAR agonists’) can be small organic molecules that bind and activate NPAR, and can be identified by assays known by those of skill in the art” (*id.*). In addition, Appellants contend that the “peptide of amino acid sequence SEQ ID NO:6 can be used as the starting point for making and testing variants” (*id.*). In particular, Appellants argue:

Where assays to identify the molecules of the claims are known, as referred to in the specification, are relatively uncomplicated to those of skill in the art, and have a high probability of success in yielding molecules that satisfy the requirements of the claims, the quantity of experimentation is not undue, and the breadth of the claims is appropriate.

(*Id.* at 5.)

We are not persuaded. SEQ ID NO: 6 has the “amino sequence of SEQ ID NO: 5 and also contains a C-terminal amide” (FF 14). SEQ ID

NO: 5 is “a fragment of human thrombin corresponding to prothrombin amino acids 508-530” (FF 5). Assuming that SEQ ID NO: 6 could be used as a starting material for making and testing peptide variants, we do not agree that Appellants have shown that knowledge that SEQ ID NO: 6 is an NPAR agonist provides sufficient guidance for one of ordinary skill in the art to make non-peptide small organic molecules that bind and stimulate NPAR, without undue experimentation. In particular, we do not agree that the Specification provides sufficient guidance to determine which such molecules should be subjected to the screening assays identified in the Specification in order to identify molecules that bind and stimulate NPAR.

Conclusion of Law

Appellants have not rebutted the Examiner’s prima facie case that the Specification does not enable the full scope of NPAR agonists recited in claim 1. We therefore affirm the enablement rejection of claim 1. Claims 2-10, 13-16, and 21-24 fall with claim 1.

ORDER

We affirm the written description and enablement rejections of claims 1-10, 13-16, and 21-24.

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

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