

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 48

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEVEN S. GROSS

Appeal No. 1996-3326
Application No. 08/063,067

HEARD: April 19, 2000

Before KIMLIN, WALTZ, and KRATZ, Administrative Patent Judges.
WALTZ, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 12, which are the only claims in this application.

According to appellant, the invention is directed to two embodiments. The first embodiment involves the administration of known groups of tetrahydrobiopterin synthesis antagonists

to subjects under cytokine therapy for the prophylaxis or treatment of systemic hypotension caused by pathological overproduction of nitric oxide from arginine in vascular cells of the subject (Brief, pages 1-2). The second embodiment involves administration of known groups of tetrahydrobiopterin synthesis antagonists to subjects for the prophylaxis or treatment of systemic hypotension caused by pathological overproduction of nitric oxide from arginine induced in vascular cells in said subject by bacterial endotoxins (Brief, page 2). A copy of illustrative claims 1 and 6 is attached as an Appendix to this decision.

The examiner has relied upon the following references¹ as evidence of obviousness:

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| Austel et al. (Austel) 1987 | 4,670,438 | Jun. 2, |
| Nichol et al. (Nichol) 1987 | 4,701,455 | Oct. 20, |
| Spada et al. (Spada) 1991 | 5,002,944 | Mar. 26, |

¹The examiner has listed #1227 and #7834 from the Merck Index as "prior art of record relied upon in the rejection of claims under appeal" (Answer, page 2). However, we do not find this reference applied against any claims in any rejection in the Answer.

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Ayling et al. (Ayling) 84/04040 Oct. 25,
1984
(Published International Application)

Rees et al. (Rees), *Chemical Abstracts*, 110:112347q (1989)

Kwon et al. (Kwon),² "Reduced Biopterin as a Cofactor in the
Generation of Nitrogen Oxides by Murine Macrophages," *J. Biol.
Chem.*, Vol. 264, No. 34, pp. 20496-20501 (Dec. 5, 1989).

Salvemini et al. (Salvemini),³ *Chemical Abstracts*, 115:204139e
(1991).

Claims 1 through 12 stand rejected under 35 U.S.C. § 103
as unpatentable over Rees, Salvemini and Kwon in view of
Ayling, Spada, Nichol and Austel (Answer, page 4).⁴ We
reverse this rejection for reasons which follow.

²The examiner, on page 2 of the Answer, lists the abstract
of this article as part of the prior art of record relied upon
in the rejection ("111CA:230525q") but subsequently employs
the full article as a basis for the § 103 rejection (see the
Supplemental Answer dated Mar. 1, 1995, Paper No. 35).

³This reference is listed as prior art on page 2 of the
Answer under the name "Salverini" while recited as "Salvemin"
in the rejections on pages 3 and 4 of the Answer. For
purposes of this decision, we refer to and cite this reference
under the name recited in *Chemical Abstracts*, i.e., Salvemini.

⁴The final rejections of claims 1-12 under the first
paragraph of 35 U.S.C. § 112 and claims 1-12 under 35 U.S.C.
§ 102(b) as anticipated by Rees or Salvemini or Kwon or Spada
or Nichol or Austel have been withdrawn by the examiner on
page 1 of the Supplemental Answer dated Mar. 1, 1995, Paper
No. 35 (see also the Answer, pages 1-2).

OPINION

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Furthermore, in construing the scope of the claims, the examiner must give effect to all claim limitations. *See In re Angstadt*, 537 F.2d 498, 501, 190 USPQ 214, 217 (CCPA 1976). Therefore the locus or population of subjects that is treated in the method of the claims on appeal is limited to those subjects with hypotension caused by pathological overproduction of nitric oxide from arginine induced in vascular smooth muscle cells by therapy with cytokine (claim 1) or by bacterial endotoxins (claim 6).

The examiner finds that the teachings of Kwon "would have motivated the skilled artisan, charged with treating hypotension to reduce cellular NO₂ levels by inhibiting the activity of dihydrofolate reductase." (Supplemental Answer, page 5). However, the examiner has not rebutted appellant's argument that Kwon is directed only to the generation of nitrogen oxides in *murine macrophages*, not vascular cells (see

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the Supplemental Reply Brief dated Mar. 24, 1995, page 6).
The examiner has also not answered appellant's contention that the data in Kwon shows there is a reservoir of tetrahydrobiopterin in uninduced macrophages which is greater than that necessary for producing maximal generation of nitric oxide, thus leading away from inhibiting the induction of tetrahydrobiopterin to reduce nitric oxide synthesis (Supplemental Reply Brief, page 2).

The other primary references to Rees and Salvemini do not remedy the deficiencies noted above with regard to Kwon. Rees is directed to the blocking of NO production by L-NMMA while Salvemini, like Kwon, is directed to macrophages, teaching that L-NMMA "probably inhibits NO formation from L-arginine." (See the Answer, page 5).

The examiner finds that the secondary references to Spada, Nichol and Austel "teach various pterion analogs and homologs as useful for treating various cardiac conditions to include hypotension." (Answer, page 5). We agree with appellant (Brief, pages 24-25) that this finding is an overgeneralization. The compounds of Austel lower blood pressure (column 12, lines 17-22) which is the opposite effect

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of the claimed method. The compounds of Nichol may be used to treat "orthostatic hypotension" and other diseases caused by a deficiency of catecholamines and serotonin (column 1, lines 6-16; column 3, lines 1-5; and column 4, lines 55-61). Thus Nichol is not concerned with hypotension due to cytokine therapy or bacterial endotoxins. Spada does not disclose treatment of hypotension but is directed to compounds with cardiogenic properties (column 1, lines 9-16; lines 35-37; column 2, lines 45-47; and column 14, lines 40-42).

The examiner finds that Ayling teaches "various methods by which pterin [sic] cofactors mediate the enzyme systems responsible for biological nitric oxide production." (Answer, page 5). As noted by appellant on page 23 of the Brief, Ayling is directed to treating conditions stemming from a deficiency in tetrahydrobiopterin by providing a substitute and does not suggest blocking its induction (see Ayling, page 16).

For the foregoing reasons, we determine that the examiner's conclusion of obviousness is not supported by the facts. Therefore the examiner has not presented a *prima facie* case of obviousness. In view of this determination, we need

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not reach the issue of the sufficiency of the declaration evidence (see the Stuehr and Gross Declarations under 37 CFR § 1.132 dated Nov. 15, 1993, attached to Paper No. 22). *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Accordingly, the rejection of claims 1 through 12 under 35 U.S.C. § 103 is reversed.

The decision of the examiner is reversed.

OTHER ISSUES

Upon the return of this application to the jurisdiction of the examiner, the examiner and applicant should consider the patentability of the claims under the judicially created doctrine of obviousness-type double patenting in light of recently issued patents to applicant (see at least U.S. Patents 5,502,050; 5,874,433; 5,877,176; and especially claims 7 and 9 of U.S. Patent No. 5,880,124).

REVERSED

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| EDWARD C. KIMLIN |) | |
| Administrative Patent Judge |) | |
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| |) | BOARD OF PATENT |
| THOMAS A. WALTZ |) | APPEALS |
| Administrative Patent Judge |) | AND |
| |) | INTERFERENCES |
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| PETER F. KRATZ |) | |
| Administrative Patent Judge |) | |

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APPENDIX

Claim 1. A method of prophylaxis or treatment of a subject for systemic hypotension caused by pathological overproduction of nitric oxide from arginine induced in vascular smooth muscle cells in said subject by therapy of said subject with a cytokine, said method comprising administering to said subject of a therapeutically effective amount of (a) at least one guanosine triphosphate pathway tetrahydrobiopterin synthesis antagonist which is not a reduced pterin that is a substrate for the pterin salvage pathway or (b) at least one dihydrofolate reductase inhibitor or both (a) and (b), thereby to inhibit nitric oxide synthesis in said cells to ameliorate said hypotension.

Claim 6. A method of treatment of a subject for systemic hypotension or expected systemic hypotension caused by pathological overproduction of nitric oxide from arginine induced in vascular smooth muscle cells in said subject by bacterial endotoxins, said method comprising administering to said subject of a therapeutically effective amount of (a) at least one guanosine triphosphate pathway tetrahydrobiopterin synthesis antagonist which is not a reduced pterin that is a substrate for the pterin salvage pathway or (b) at least one dihydrofolate reductase inhibitor or both (a) and (b), thereby to inhibit nitric oxide synthesis in said cells to ameliorate said hypotension.

Leticia

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APJ WALTZ

APJ KRATZ

APJ KIMLIN

DECISION: REVERSED
Send Reference(s): Yes No
or Translation (s)
Panel Change: Yes No
Index Sheet-2901 Rejection(s):
Prepared: September 18, 2001

Draft Final

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OB/HD GAU

PALM / ACTS 2 / BOOK
DISK (FOIA) / REPORT