

Filed on behalf of Gnosis S.p.A., Gnosis Bioresearch S.A. and Gnosis U.S.A., Inc.

By: Jonathan J. Krit

Janine A. Moderson

AMIN TALATI, LLC

55 West Monroe Street, Suite 3400

Chicago, Illinois 60603

Tel.: (312) 466-1033

Fax: (312) 884-7352

Email: patent@amintalati.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GNOSIS S.p.A., GNOSIS BIORESEARCH S.A. and GNOSIS U.S.A., INC.
Petitioners

v.

Patent Owner of
U.S. Patent 6,011,040 to Muller et al.
Appl. No. 09/095,572 filed June 11, 1998
Issued Jan. 4, 2000

IPR Trial No. TBD

DECLARATION OF JOSHUA W. MILLER, Ph.D.

I. INTRODUCTION

1. I, Joshua W. Miller, have been retained by counsel to provide an expert opinion on behalf of Gnosis SpA in the above-captioned matter. I reviewed the following patents prior to preparing this declaration: U.S. Patent Nos. 5,997,915 ("the '915 patent")(Ex. 1001); 6,673,381 ("the '381 patent")(Ex. 1002); 7,172,778 ("the '778 patent")(Ex. 1003) and 6,011,040 ("the '040 patent")(Ex. 1004). I reviewed each of the references cited in this declaration.

II. QUALIFICATIONS

2. I earned my master's degree (M.S.) and my doctoral degree (Ph.D.) in nutrition from the Tufts University School of Nutrition in 1990 and 1993, respectively. My doctoral dissertation was an investigation of the pathogenesis of hyperhomocysteinemia caused by B vitamin deficiencies, including folate deficiency.

3. After consecutive post-doctoral experiences at the USDA Human Nutrition Research Center on Aging in Boston, MA, and in the Department of Pharmacology at the Duke University Medical Center in Durham, NC, I joined the faculty of the University of California, Davis, School of Medicine in 1997 as Assistant Professor in the Department of Medical Pathology and Laboratory

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Medicine. In 2004, I was promoted to Associate Professor, and in 2011 I was promoted to Professor with tenure. In 2012, I moved to Rutgers University in New Jersey to serve as Professor in the Department of Nutritional Sciences. As of July 1, 2013, I will assume the position of Chair of this department.

4. My research focuses on the relationships among B vitamins (folate, B12, B6), homocysteine, and various degenerative disorders, including neurodegenerative diseases (Alzheimer's and Parkinson's), cancer, and sickle cell disease.

5. I am the author of over 60 peer-reviewed publications and 30 reviews, book chapters, and editorials. I have given over 30 oral presentations as an invited speaker for both national and international meetings. I have served as a manuscript reviewer for over 70 journals and as a grant reviewer for 12 funding agencies.

6. I served as a member of the Working Group on Folic Acid Analysis and Sufficiency for Reproductive Outcomes for the March of Dimes in 1999 and the Working Group on Vitamin B12 Fortification for the Second Technical Workshop on Wheat Flour Fortification in 2008. I currently am a member of the American Society for Nutrition, the Vitamin B12 Working Group on Biomarkers of Nutrition for Development (BOND) for the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Medical Advisory Board for the Diabetes Action Research and Education Foundation.

7. Further details concerning my background, training, experience and listing of publications within the last ten years are contained in my *curriculum vitae* (Ex. 1006).

III. BACKGROUND

8. The term "reduced folate" as used in the '915, '381 and '778 patents refers to the enzymatic reduction of the non-naturally occurring compound folic acid (pteroyl-L-glutamic acid), which the human body metabolizes to tetrahydrofolic acid or one of its one-carbon units of oxidation: 5-methyl-tetrahydrofolic acid, 5-formyl-tetrahydrofolic acid, 10-formyl-tetrahydrofolic acid, 5,10-methylene-tetrahydrofolic acid, 5,10-methenyl-tetrahydrofolic acid, and 5-formimino-tetrahydrofolic acid. The term "5-MTHF" was generally understood before 1996 to refer to the racemic form of 5-methyl-tetrahydrofolic acid. With respect to the 5-methyl-tetrahydrofolic acid and 5-formyl-tetrahydrofolic acid, the 6(S) notation refers to the natural stereoisomer of those compounds.

9. I have been asked to provide my opinion on the level of ordinary skill in the art in the January 1996 time frame pertaining to the use of the reduced folates described in the '915, '381, '778 and '040 patents. I understand from counsel that January of 1996 represents the earliest patent application to which any

of the asserted patents claim any sort of priority. In my opinion, a person of ordinary skill in the art relevant to the claims would have been at least a graduate of a master's graduate degree program which meaningfully studied folates, or have had at least five years of meaningful scientific experience in the relevant area of folates.

IV. THE SERFONTEIN REFERENCE AS IT RELATES TO ANTICIPATION OF CERTAIN U.S. PATENTS

10. European Patent Application Publication No. 595,005 A1, was submitted by inventor, Willem Serfontein, and published in 1994 ("the Serfontein reference") (Ex. 1009). The Serfontein reference discloses a composition for lowering homocysteine in humans that includes vitamins B6, B12 and an "active metabolite of folate" which is a phrase one of ordinary skill in the art would recognize to constitute a genus of no more than eight compounds, including folinic acid also known as 5-FTHF or leucovorin, and 5-methyltetrahydrofolic acid also known as 5-MTHF. One with ordinary skill in the art also would have recognized 5-MTHF to be a racemic mixture that includes the biologically active isomer 6(S)-5-MTHF ("the S isomer") and the biologically inert isomer 6(R)-5-MTHF ("the R isomer"). The cover page of the Serfontein reference summarizes one embodiment

of its claimed invention as follows:

- ⑤ Pharmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising:
- a) vitamin B6;
 - b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo;
 - c) vitamin B12, with or without intrinsic factor
- and optionally antioxidants, choline and/or betaine. a) and b) are provided in slow release form (2-8 hours) and c) is to be released immediately (within 20 minutes).

(Serfontein, p. 1)

11. In addition to pharmaceutical preparations, Serfontein discloses that his invention can be used in dietary preparations, "Here pharmaceutical and dietary preparations are disclosed..." (p. 4, ln. 24) "The dosage regimen may be programmed to be optionally adapted to a predetermined daily dietary programme." (p. 5, ln. 46-47)

12. The Serfontein embodiment containing "a suitable active metabolite of folate" is highlighted as one of the only embodiments on the cover page and in the very first two independent claims in the patent application. (pp. 1, 18)

13. Preceding the Serfontein reference was European Patent Application Publication No. 388,827 A1, by inventor Cristina Le Grazie, and published in 1990 ("the Le Grazie reference") (Ex.1010). The Le Grazie reference refers to the "Use of 5-methyltetrahydrofolic acid, 5-formyltetrahydrofolic acid and their pharmaceutically acceptable salts in the preparation of pharmaceutical compositions in controlled release form active in the therapy of organic mental disturbances, and the relative pharmaceutical compositions." (p. 1, ln. 1-5)

14. The Le Grazie reference defines the term "5-methyltetrahydrofolic acid" and the initials of "MTHF" as including both the racemic form of 5-MTHF and its natural isomer, 6(S)-5-MTHF. (p. 2, ln. 8-10)

15. The Le Grazie reference discloses "...pharmaceutical compositions of controlled-release type, with an active principle release time varying from 15 minutes to 8 hours and preferably varying from 20 to 60 minutes, and containing from 5 to 200 mg and preferably 10 to 50 mg of MTHF or FTHF or their pharmaceutically acceptable salts...to treat subjects affected by organic mental disturbances." (p. 2, ln. 39-43)

16. The Le Grazie reference further states that, "In the central nervous system the folates and in particular MTHF participate in basic biochemical processes by intervening in the synthesis of S-adenosyl-L-methionine (SAME)...." (p. 2, ln. 29-31) One of ordinary skill in the art would recognize that this effect of MTHF to promote SAME synthesis necessarily requires homocysteine as a substrate and that utilization of homocysteine for this purpose would likely reduce intracellular and blood homocysteine concentrations.

17. The Le Grazie reference further states that, "In the circulating blood the folate pool is mostly represented by MTHF, but also by FTHF. MTHF represents the main form of folate transport in the blood." (p. 2, ln. 26-28)

18. Modern Nutrition in Health and Disease, 7th Ed. (1988) was a well-known publication that served as the primary textbook for me and my fellow graduate students in the Tufts University School of Nutrition in the late 1980s and early 1990s. In the chapter titled "Folic Acid and Vitamin B12", authored by two prominent nutrition researchers, Victor D. Herbert and Neville Colman, the biochemistry and metabolism of the active metabolites of folic acid are described within the text and in Figure 21-4. (Ex. 1007) Though these authors use shorthand nomenclature in their chapter for each of the active metabolites of folic acid, they do reference the International Union of Pure and Applied Chemistry (IUPAC) and International Union of Biochemistry (IUB) Joint Commission on Biochemical Nomenclature (JCBN) recommendations for nomenclature for folic acid and related compounds. These recommendations, published in 1986 (<http://www.chem.qmul.ac.uk/iupac/misc/folic.html>), include nomenclature for the "natural stereoisomers" of the active metabolites. (Ex. 1008) These active metabolites include:

a) 6(S)-5-Methyltetrahydrofolate (6(S)-5-MTHF) – the primary form of folate found in the blood and the methyl donor for the conversion of homocysteine to methionine within cells.

b) 6(S)-5,6,7,8-Tetrahydrofolate (6(S)-THF) – a product of several folate-dependent cellular reactions, including the conversion of homocysteine to methionine, the biosynthesis of formate, and the reduction of folic acid.

c) 6(R)-5,10-Methylenetetrahydrofolate (6(R)-5,10-MethyleneTHF) – an intermediate that participates in the synthesis of thymidylic acid (used for the synthesis of DNA), is converted to 6(S)-5-FTHF (see below), or is converted to 6(S)-5-MTHF.

d) 6(S)-5-Formyltetrahydrofolate (6(S)-5-FTHF; also known as folinic acid and leucovorin) – an intermediate used in the synthesis of purines (adenine and guanine) for DNA and RNA synthesis. 6(S)-5-FTHF is also used as a means to save patients from the potential lethal toxicity of anti-folate cancer drugs (often referred to as the "leucovorin rescue").

19. The four additional active metabolites include the following:

a) 6(R)-10-Formyltetrahydrofolate (6(R)-10-FTHF) – an intermediate metabolite involved in purine synthesis.

b) 6(R)-5,10-Methenyltetrahydrofolate (6(R)-5,10-methenylTHF) – an intermediate metabolite in the interconversion of 6(S)-THF and 6(R)-5,10-MethyleneTHF, and in histidine catabolism.

c) 6(S)-5-formiminotetrahydrofolate (6(S)-formiminoTHF) – a second intermediate metabolite in the interconversion of 6(S)-THF and 6(R)-5,10-MethyleneTHF, and in histidine catabolism.

d) 7,8-Dihydrofolate (DHF) – an intermediate metabolite in the conversion of folic acid to 6(S)-THF, the conversion of 6(R)-5,10-MethyleneTHF to 6(S)-THF, and the synthesis of thymidylic acid for DNA synthesis. (Ex. 1008, Table 2.8)

20. Therefore, the active metabolites of folic acid in humans is a group of no more than eight members.

21. A person of ordinary skill in the art also would have understood that only 6(S)-5-MTHF and 6(S)-5-FTHF were the active metabolites of folate *suitable* for consumption by humans as oral supplements. For example, in European Patent Application Publication No. 627,435 A1, inventor Ambrosini ("the Ambrosini reference") (Ex. 1011) previously disclosed "a method for the industrial preparation of 5-(methyl)-(6S)-tetrahydrofolic acid and 5-formyl-(6S)-tetrahydrofolic acid herein referred as 'MTHF' and 'FTHF.' ' MTHF and FTHF are physiological molecules which together with the less stable 6,10-methylenetetrahydrofolic and tetrahydrofolic acids constitute the in vivo active forms of folic acid, commonly named as folic acid co-factors. From the therapeutical point of view, both MTHF and FTHF find an application in all of the

forms of folate deficiencies, as general liver protective, and more recently, in antitumor therapies." (Ambrosini, p. 2, ln. 4-8) Ambrosini further discloses that, "Usually it is well known that when there exist stereoisomeric pharmaceutical forms, only one of them is active, the other being inactive or even harmful. In the present case, it is well known that the active forms are the 6(S) ones." (Ambrosini, p. 2, ln. 30-33)

22. U.S. Patent No. 5,194,611 to inventor Marazza ("the Marazza reference") also disclosed the preferred use of the natural 6(S)-5-MTHF isomer to address folate deficiency states because it was assumed that the unnatural 6(R)-5-MTHF was inert, was excreted in an unchanged form and could interfere with the folate transport system through cell membranes in humans. (Marazza, Col. 1, ln. 25-28; Col. 2, ln. 3-32) (Ex. 1012)

23. Claims 11 through 16 of the '040 patent contain the limitations of "wherein increased levels of homocysteine in the human body are associated with...methylene tetrahydrofolate reductase deficiency..." or "...thermolabile methylene tetrahydrofolate reductase deficiency...." (Ex. 1004, col. 6)

24. Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (p.3, lines 20-23)

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25. The statement regarding the enzyme defect in the transsulfuration pathway would be understood by one of ordinary skill in art as a reference to cystathionine β -synthase deficiency.

26. The statement regarding the enzyme defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine would be understood by one of ordinary skill in the art as a reference to methylene tetrahydrofolate reductase deficiency, a thermolabile methylene tetrahydrofolate reductase defect, or deficiency in one of the enzymes required for the synthesis of methylcobalamin (a cofactor form of vitamin B12) required for the 5-methyl tetrahydrofolate-dependent conversion of homocysteine to methionine.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: January 23, 2013


Dr. Joshua W. Miller