

UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE PATENT TRIAL AND APPEAL BOARD

-----x  
GNOSIS S.P.A., GNOSIS  
BIORESEARCH S.A., AND  
GNOSIS U.S.A., INC.,

Petitioners,

Case IPR2013-00117  
US Patent 6,011,040

v.

MERCK & CIE,

Patent Owner.

-----x

DEPOSITION OF JESSE F. GREGORY, III, Ph.D.

Wednesday, November 13, 2013

New York, New York

9:00 a.m.

Reported by:  
Maureen Ratto, RPR, CCR, CLR  
Job No. 32419

Gnosis Ex. 1135

Gnosis v. Merck/SAMSF  
IPR2013-116,-117,-118,-119

1 GREGORY

2 It is the trapping mechanism that  
3 retains folate in a cell, and so folic  
4 acid is reduced quickly to  
5 tetrahydrofolate, THF, which is then  
6 the outstanding substrate for  
7 polyglutamate synthesis. So, that's  
8 the important mechanism, it's the  
9 reduction of folic acid.

10 And so, 5-methyl is not a good  
11 substrate. And so, the fact that  
12 they're both folic acid and 5-methylTHF  
13 poor substrates, is really not an  
14 important comparison.

15 Q. Okay. Would you agree it was  
16 known prior to 1996, that folic acid  
17 were -- was a poor substrate for the  
18 synthesis of polyglutamates?

19 A. I don't know.

20 Q. Did you -- so I assume you  
21 didn't research that question either in  
22 preparing your Declaration, correct?

23 A. I didn't look at that  
24 literature, specifically, prior to my  
25 Declaration. I believe it was known,

1 GREGORY

2 but I didn't go back and read the  
3 literature on polyglutamylation  
4 enzymes.

5 Q. Doctor, I've handed you a  
6 document we've marked as Exhibit 1016.  
7 This is a document which contains, I  
8 guess we would call it a letter in the  
9 British Medical Journal.

10 (Whereupon, the Deponent reviews  
11 the document.)

12 Q. I'd like you to take a look at  
13 the letter that is in the box on the  
14 first page with the listed author of  
15 Patricia Barford.

16 Do you see that?

17 A. Barford and Ann Pheasant, yes.

18 Q. And you have reviewed this  
19 letter before, correct?

20 A. I have read it before, yes.

21 Q. The --

22 A. Sorry. I need to read it.

23 (Whereupon, the Deponent reviews  
24 the document.)

25 MR. MALIK: Counsel, I will note

1 GREGORY

2 document we've marked as Exhibit 1080.

3 It's an article titled "Mammalian  
4 Folial Polyglutamate Synthetase to  
5 Substrate-Specificity in Kinetic  
6 Properties."

7 A. What it's actually saying is --  
8 the title is: "Mammalian Folial  
9 Polyglutamate Synthetase," not  
10 synthesis.

11 Q. Okay. Thank you for that  
12 correction.

13 The first listed author is a  
14 Cichowicz, and the second listed author  
15 is a Dr. Shane.

16 Doctor, have you reviewed this  
17 article before?

18 A. Yes. This is the Shane article  
19 that I referred to earlier that dealt  
20 with the enzymatic properties of folial  
21 polyglutamate synthetase and compared  
22 the substratability of various folates.

23 Q. Okay. I'd like you to turn to  
24 515 and Table 6.

25 In Table 6, it's titled "Folate

1 GREGORY

2 Compounds as Substrates for Folial  
3 Polyglutamate Synthetase," and you see  
4 under the "Substrate" there is a line  
5 for "PteGlu," which we know is folic  
6 acid?

7 A. Yes.

8 Q. Okay. And for the "10  
9 micromolar column," do you see there is  
10 a reading of "5.7"?

11 A. Yes. These are units of just  
12 relative activity.

13 Q. Okay. And under "Substrate," do  
14 you see there's also a line for the  
15 5-MTHF, which is the called  
16 "(6RS)5-methyl-H4-PteGlu."

17 Do you see that?

18 A. Right.

19 Q. And that indicates a level of  
20 "10" under the "10 micromolar" column,  
21 correct?

22 A. Yes.

23 Q. And looking at the "50  
24 micromolar" column, we have a relative  
25 activity of 17 for folic acid, correct?

GREGORY

A. Right.

Q. And for the 5-MTHF we have a relative activity of 36, correct?

A. Yes. This indicates they're both bad substrates.

Q. Okay. But you would agree that it does show that 5-MTHF is a better substrate in comparison to folic acid, correct?

A. What it shows is that they're bad substrates and it's a little bit -- of the two bad substrates, the 5-MTHF is a little better, but still a bad substrate.

Also, the "50 micromolar" column is, you know, certainly a valid experiment but it's not predictive because 50 micromolar is not the range of liver folate concentration.

[REDACTED]

GREGORY

[REDACTED]

Q. Prior to 1996, were you aware of any reduced folates available to research for use in therapeutic use and I think that you indicated that you've used some?

A. Yes.

Q. Some of the (6S)5-MTHF, correct?

MR. MALIK: Asked and answered.

1 GREGORY

2 A. Well, in two different  
3 applications. One, is laboratory  
4 chemicals for analytical standards were  
5 commercially available quite a long  
6 time before that and not suitable for  
7 use in humans. In the context of my  
8 own experiment in the 1992 paper, that  
9 was work that was approved for me to  
10 synthesize and use in a small  
11 experimental setting. They were  
12 certainly not available for routine use  
13 or therapeutic use.

14 Q. Okay. Prior to 1996, were you  
15 aware of any other reduced folates that  
16 were available for therapeutic use?

17 A. Well, the field of cancer  
18 chemotherapy with antifolates generally  
19 involves the use of folinic acid folate  
20 rescue, so you give a toxic dose of an  
21 antifolate and then it's followed  
22 somewhat later by a rescue to preserve  
23 the non-cancerous cells.

24 Q. Okay. So, that's two reduced  
25 folates. Any more that you can think



1 GREGORY

2 of?

3 MR. MALIK: Mischaracterize his  
4 prior testimony.

5 A. Which two were you --

6 Q. I'm just trying to understand,  
7 you know, what reduced folates were you  
8 aware of prior to 1996, that could be  
9 used for therapeutic use?

10 A. I'm not sure I said two. I said  
11 the use of 5-formylTHF in cancer  
12 chemotherapy.

13 Q. Okay. And then you said, "the  
14 (6S)5-MTHF was used in your 1992" --

15 A. That was not therapeutic use --

16 Q. -- report?

17 A. -- that was a research study  
18 using very small amounts of stable  
19 isotope labeled deuterium, was the  
20 word, labeled folates.

21 Q. Okay.

22 A. It's absolutely not therapeutic.

23 Q. Okay.

24 A. So back to your question, I gave  
25 you an example, one use for therapeutic

1 GREGORY

2 use.

3 Q. Okay. Was the racemic 5-MTHF  
4 available for therapeutic use prior the  
5 1996, to your knowledge?

6 MR. MALIK: Incomplete  
7 hypothetical.

8 A. I'm not a clinician. It's my  
9 understanding that probably all of that  
10 5-MTHF -- when you say -- what did you  
11 say FTHF?

12 Q. 5-MTHF, the --

13 A. 5-MTHF?

14 Q. -- the racemic?

15 A. Oh, the racemic? I don't know  
16 of its commercial status, so I can't  
17 comment on that.

18 Q. Okay. Are you aware of any  
19 other reduced folates that were used  
20 for therapeutic use prior to 1996?

21 A. No. I'm not aware of any.

22 Q. Okay. Doctor, I've handed you  
23 what we've marked as Gnosis Exhibit  
24 1009. It's European patent  
25 application, Publication No. 0,595,005.

GREGORY

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Q. Would you agree that prior to 1996, a POSA would know that the free acid forms of folate need to be turned into a salt form to be therapeutic?

MR. MALIK: Incomplete hypothetical. Calls for speculation.

A. Yeah, and in hindsight, I think that a person of ordinary skill in the art would not have really considered

1 GREGORY

2 the salt forms that -- that just  
3 wouldn't have been, you know, in common  
4 understanding or consideration.

5 Q. Okay. Let's look at the  
6 Ambrosini reference. It's one of the  
7 European patent applications.

8 A. Okay. I got it.

9 Q. If we can look at page 3, and  
10 starting on line 29, it's a sentence  
11 we've already looked at. Line 29, page  
12 3 says, "As to the practical  
13 therapeutic use, (6S)5-MTHF and  
14 (6S)FTHF are not used, per se, but as  
15 salts, usually calcium salts."

16 A. Yes. That is what Ambrosini  
17 says. You are asking me what a POSA  
18 would understand and I don't think the  
19 implications of salt form would have  
20 been common knowledge. I was aware of  
21 various salt forms just because when I  
22 buy a laboratory chemical form of a  
23 reduced folate I have to choose between  
24 calcium and barium and sodium and  
25 potassium salts that were all available

1 GREGORY

2 at catalogue at the time. It wouldn't  
3 have been clear for therapeutic use,  
4 the pros and cons of various forms or  
5 the free acid form.

6 Q. In addition to pharmaceutical  
7 preparations, do you agree that  
8 Serfontein discloses dietary  
9 preparations?

10 A. Serfontein? My understanding is  
11 he was referring to oral supplements as  
12 one of their applications -- one of his  
13 applications. So, if you consider that  
14 a dietary supplement, yes. I don't  
15 think he was talking about food  
16 fortification in any context.

17 Q. Okay. Let's look at page 4 of  
18 Serfontein. Page 4, line 24, there is  
19 a sentence that begins, "Pharmaceutical  
20 and dietary preparations are disclosed  
21 for the treatment or prophylaxis of  
22 elevated homocysteine or methylthionine  
23 levels in the blood of human infants  
24 and pathological disturbance connected  
25 therewith," and the sentence continues.

1 GREGORY

2 program.

3 Q. Counsel also said there is --  
4 strike that.

5 Counsel for Gnosis also noted  
6 there was no data or reference  
7 citations in Goodman and Gilman.

8 Do you recall that conversation?

9 A. Yes.

10 Q. The fact that there is no data  
11 or referenced citations, does that in  
12 any way, diminish the value of Goodman  
13 and Gilman?

14 MR. CWIK: Objection. Asked and  
15 answered.

16 A. Not in the least. It's a very  
17 authoritative source.

18 Q. Let me direct your attention to  
19 paragraph 29 of your report.

20 A. Okay.

21 Q. I want to be clear, as far as  
22 your testimony today.

23 Earlier today you said that  
24 Goodman and Gilman in the excerpt cited  
25 does not explicitly make reference to

1 GREGORY

2 5-MTHF.

3 Do you recall that?

4 A. Yes, I do.

5 Q. A person of ordinary skill in  
6 the art wouldn't just consider Goodman  
7 and Gilman in a vacuum, would they?

8 A. Not at all.

9 Q. They would consider it in  
10 connection with other information,  
11 correct?

12 A. Yes, they would.

13 Q. And some of the other  
14 information would be some of the other  
15 information directed towards reduced  
16 folates, such as the bioavailability  
17 and the other concerns you highlight in  
18 paragraph 29 and 30, correct?

19 A. Yes. Absolutely.

20 Q. So, Goodman and Gilman are part  
21 of the puzzle, correct?

22 A. It's --

23 MR. CWIK: Objection to form.

24 A. It's a part. It's an important  
25 part.

1 GREGORY

2 Q. It's part of the puzzle that  
3 would influence a POSA's thinking in  
4 1996, as to whether or not they would  
5 want to use any reduced folate,  
6 correct?

7 MR. CWIK: Objection to form.

8 A. I -- I think a POSA would read  
9 Goodman and Gilman and certainly have  
10 cause for concern.

11 Q. Okay. And if you look at  
12 paragraph 29, where you say "The  
13 caution directed to  
14 5-formyltetrahydrofolic, coupled with  
15 the other concerns highlighted within  
16 this report concerning reduced folates,  
17 particularly 5-methyltetrahydrofolate,  
18 would have dissuaded a POSA from using  
19 any reduced folate, let alone a  
20 substantially chirally pure reduced  
21 folate as a folate supplement for  
22 treating folate deficiency."

23 Do you see that sentence?

24 A. Yes, I see it. That is my  
25 opinion.