EXHIBIT
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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN, INC.,

Plaintiff,

v.

F. HOFFMANN-LA ROCHE, LTD., ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE, INC.

Defendants.

Civil Action No. 05-CV-12237 WGY

CONTAINS CONFIDENTIAL INFORMATION SUBJECT TO PROTECTIVE ORDER

EXPERT REPORT OF DR. LOWE

I, JOHN LOWE, M.D., declare as follows:

I offer this expert report on whether the claims asserted against Roche from certain of Amgen's United States Patents, as described below, are invalid for obviousness and lack of novelty.

I. QUALIFICATIONS

1. I am currently the Professor and Chair of the Department of Pathology at Case Western Reserve University School of Medicine in Cleveland, Ohio. I have held this position since March 1, 2005. Prior to March 1, 2005, I was a Professor of Pathology at the University of Michigan Medical School, and was an Investigator of the Howard Hughes Medical Institute. I held the medical school faculty position at the University of Michigan and my position with the Howard Hughes Medical Institute since October 1, 1986. In my prior position at the University of Michigan, I spent approximately 80% of my time and effort in scientific research activities. In

oligonucleotide probes based on known portions of the amino acid sequence. In a genomic library, because of the presence of "introns" or intervening non-coding sequences, the DNA sequence corresponding to any particular internal sequence of amino acids may not necessarily be represented as a contiguous DNA sequence in the library.

72. Whitehead (1983) demonstrated one could obtain a high degree of specificity using even a highly degenerate probe to screen a cDNA library for a low abundance clone. The study describes the successful isolation of a cDNA clone for a human protein, complement component C4 from a human liver plasmid cDNA library. To screen the library, the authors used a fully degenerate mixture of 384 different 23-nucleotide oligonucleotides containing all 384 possible sequences that would code for residues 14-21 of the published amino acid sequence of the human protein. One hundred sixty five clones from approximately 50,000 screened hybridized specifically to the oligonucleotide pool. Sixteen clones were selected and purified for further analysis. 12 of these 16 clones, including the clone confirmed to correspond to the first 21 amino acids of the C4 protein, contained cDNA inserts that cross-hybridized with each other under high stringency conditions indicating that most of the clones identified by screening contained C4 DNA sequences, despite the complexity of the probe mixture used to screen the library. The overall frequency of positive clones in the library demonstrated the utility of using a highly degenerate probe to screen low abundance clones.

D. It would have been obvious to generate suitable degenerate probes for screening a cDNA library from information about the amino acid sequence of tryptic fragments of the EPO protein

73. Example 1 of the Lin patents shows 17 discrete fragments of purified urinary EPO obtained from Dr. Goldwasser. (*See, e.g.,* '868 patent, cols. 15-16, and Table I; *see also* Lin Depo. Tr. (3/28/07) at 148-56; Goldwasser Depo. Tr. (2/14/07) at 216-21). These tryptic

fragments, and the amino acid sequences derived therefrom by Dr. Por Lai at Amgen, would have been the same fragments and sequences that the skilled scientist could have routinely generated, given a sufficient supply of EPO protein. For example, Dr. Lin testified that Amgen generated its sequence data using a commercially available gas-phase sequencer manufactured by Applied Biosystems. (*See* Lin Depo. Tr. (3/28/07) at 151-52). The analysis below shows that given such sequence information, one of skill could have within a very short time designed numerous different mixed fully degenerate oligonucleotide probe sets that would have been suitable to screen a cDNA library for EPO cDNA clones. For example, Dr. Lin has testified that it took him "about an hour" to design the fully degenerate oligonucleotide probes that he used. (*See* Lin Depo. Tr. (3/28/07) at 184-85; AM-ITC 00113673). Dr. Lin chose probes based on the established codon table, just as one in the art would know how to do, to match up with the amino acid sequences of the fragments that had the least amount of degeneracy, i.e., the lowest total number of possible codons. (*See* Lin Depo. Tr. (3/28/07) at 154-58, 188-90; Lin Depo. Exs. 11 (codon table), 14 (AM-ITC 00113605-06)). As shown in the following paragraphs, to design fully degenerate probes, one would merely have to go through the amino acid sequence and use the codon table to select all the codons that correlate with each amino acid. This analysis further shows that the following probe sets could have been used for screening a cDNA library without departing from any of the methods taught in the prior art.

one would express a functional, glycosylated human erythropoietin having *in vivo* biological activity. (*See* Lin Depo. Tr. (3/29/07) at 355-57, 368).

A. Lin Adopted Obvious Methods Well Described in the Prior Art to Express the EPO Gene

98. Examples 7 through 10 of the Lin patent include data regarding the expression of the human EPO coding sequence in mammalian host cells and assays of the materials produced thereby. These data were all generated using two mammalian host cell expression systems, which prior to October 1983, were routinely used by the skilled scientist to express mammalian proteins. Examples 7 through 9 relate to transient expression, using the COS-1 monkey cell line, and Example 10 describes expression from stably transfected DHFR- CHO cell line.

99. Lin testified that the work in Example 7, relating to expression in COS cells, was done by Dr. Jeffrey Browne, another Amgen scientist. (*See* Lin Depo. Tr. (3/28/07) at 230-31, 235-36). To express the EPO DNA in COS cells, a vector had to be chosen and constructed. (*See* '868 patent at col. 23, l. 14). Dr. Lin testified that this and the other elements needed for transfection and expression in the COS cell, such as use of the SV-40 gene, were known. (*Id.* at 233-34). Indeed, in his testimony, Dr. Lin stressed just how obvious was the work in Example 7:

Q. Now, did you tell Dr. Browne's group how to do the work that's in example 7?

A. They already know how to do it. Any molecular biology – have given a piece of DNA and one to put into a vector, they know what they need to do. My associate can do it. They not even require a scientist to do it.

Q. Okay.

A. So, I mean, in general, all molecular biology know how to handle all these – all these things, yeah.

100. Similarly, Dr. Lin testified with regard to the work in Example 8 (*see* Lin Depo. Tr. (3/28/07) at 238-39:

Q. And now let's get back to example 8. Who did that work?

A. (Examining document) I believe this is done by Joan Egrie's group.

Q. Okay.

And did you tell her how to do this work that's in example 8?

A. Molecular biology for doing the radioimmunoassay, they would know how to carry out radioimmunoassay. I don't have to tell her how to do it, unless she have problem, come to me, or have problem arise -- any problem raise.

Q. Did you say "raise"?

A. Yes.

Q. "Raise." Sorry.

A . So for doing the immunoassay, any associate or scientist can do it.

101. And likewise, regarding the work in Example 9, Dr. Lin stated (*see* Lin Depo. Tr. (3/28/07) at 239-40):

A. For the in vitro assay – again, I think – I believe it's done by Joan Egrie's group. For the in vivo assay, I don't know at the time we already set our own in vivo system – it's a system in-house or not. It could be done by outside consultant. I think we, at one time – some of the assay was carried out by Peter Dukes' group at the children hospital.

Q. So did you tell anybody how to do the work that was in example 9?

A. Oh, we know – how to do this. I don't have to tell them. This is individual who – in charge of setting up this assay. They know how to do it. I don't have to tell them what to do.

Q. These in vitro and in vivo assays that are described in example 9, those were assays that were commonly known at the time; right?

A. Yes.

102. And finally, in reference to the work in Example 10, Lin testified for instance that (*see* Lin Depo. Tr. (3/28/07) at 241-252):

Q. So now let's look at example 10. We get to the CHO cells.

Q. So the CHO cells that are being used in example ten, were those CHO cells obtained from the ATCC, or were they obtained from Dr. Chasen?

A. I don't know the individual who we obtained from. But this is obtained from – I believe so – through Columbia University, yes.

Q. Okay. And now, the – you see where it talks about a DHFR negative? Do you see that?

A. Yes.

Q. That technology of using DHR [sic] negative as a selectable marker, was that known to you?

A. Yeah, it was known to – to the scientists at the time.

Q. All right. And so who did the work of putting together the EPO gene with the DHFR gene?

A. In this case, it's – again, Jeff Browne's group.

Q. Okay. And did you have to instruct them or give them any guidance on how to do this?

A. No, I don't have to. Just like I give the piece DNA to my associate, and tell them to like it or something, they wouldn't know what to do.

Q. I'm going to ask you about who did the work and the use of methotrexate just to focus you for when you read.

A. (Examining document) Yeah. This – again, this is done by Jeff Browne's group.

Q. Okay. Now, this paragraph talks about inhibiting using methotrexate. Do you see that?

A. Where is it?

Q. It's line 45, 46, 47.

A. Yes.

Q. Did you learn about how to do that from Dr. Browne?

A. This is known at the time, when you want to select cells which – let me put it this way: This methotrexate is long – is known – is known to – to inhibit dihydrofolate reductase. This is known. This is the way the people use to amplify the DHFR gene, which is known at the time.

A. The assay aspect was carried out by Joan Egrie's groups. And in terms of amplification, carry out culture, this I think is carried out by Jeff Browne's group.

Q. And did you give either of those groups instructions how to do what's in this paragraph of?

A. They already been doing this so long. I don't need to give them any instruction.

Q. And there, it says on line 25, "Standard screening procedures are being employed in an attempt to isolate genetically homogeneous clones with the highest production capacity." Do you see that?

A. Yes.

Q. Was that accurate?

A. Yes. That's what it says here, yes.

Q. And who did that work?

A. Again, this is done by Jeff Browne's group, I think.

(*See also* Lin Interference Testimony cited *infra* in paragraphs 211-16).

103. As further illustrated by the prior art described below, to express recombinant human erythropoietin Lin adopted essentially the same approach that many researchers at that time had used to express numerous mammalian glycoproteins, including a variety of human glycoproteins. Nothing in the methods Lin used to express a human glycoprotein was novel or departed in any significant way from the prior art. A skilled scientist would have found the approach Lin adopted the natural and obvious choice for expressing a human glycoprotein, and would have had a reasonable expectation that such an approach would work to express a functional *in vivo* biologically active human EPO. Dr. Lin himself held such an expectation. (*See* AM-ITC 00174334-35 at 17:12-15 ("Q. Did you accept the fact that if the gene could be cloned that it could be successfully incorporated into host cells for the purpose of expressing erythropoietin? A. Yes, I would think so. Yes."); Lin Depo. Tr. (3/29/07) at 368 ("Q. My question was, whether you had the expectation when you had the genomic EPO gene that when put into a mammalian cell and expressed, that the resulting EPO would be biologically active? [objection interposed] A. Of course, we would expect that it – to be – to have that activity – in the biological activity.")).

210. In the '096 Interference the Board of Patent Appeals and Interferences stated in their Final Judgment of December 3, 1991, 21 U.S.P.Q. 2d 1731 (AM-ITC 00265548) that:

> The record indicates that all the work at Amgen relating to expression of the EPO gene in mammalian host cells was directed and supervised by Dr. Browne, assisted by Ralph Smalling. Dr. Lin does not recall giving any instructions or suggestions as to how such expression should be carried out (PF V-3, 4). The effort to isolate the EPO glycoprotein expression product was carried out by Dr. Strickland, and Dr. Lin gave no specific instructions for accomplishing that task (PF V-6).

211. From my reading of Dr. Lin's deposition testimony of April 9, 1991 during the Interference proceedings (AM-ITC 00410931-00411088), I conclude that he only provided Dr. Browne and Ralph Smalling with the DNA sequence and provided them with no further instructions. The testimony from which I draw this conclusion (pages 205-208) reads as follows

> Q. Now, the district court decision indicates that someone other than Dr. Lin did the work with the mammalian expression system. Do you see that in the third quoted paragraph?
>
> A. That's correct, yes.
>
> Q. And that is a correct statement; right?
>
> A. That is correct, yes.
>
> Q. Now, you indicate in your declaration in paragraph 5 that the expression of EPO in the 293 cells, the COS cells, and the CHO cells was carried out by Dr. Jeff Browne?
>
> A. By Jeff Browne and his associates.
>
> Q. And his associates, one of whom was Mr. Smalling?
>
> A. That's correct, yes.
>
> Q. And in that connection, you provided Dr. Browne with a DNA sequence which included the sequence coding human EPO; is that right?
>
> A. That's correct, yes.
>
> Q. And you also provided Dr. Browne with a monkey cDNA sequence which encoded monkey EPO; is that right?
>
> A. That's correct, yes.
>
> Q. And you then requested that Dr. Browne and his colleagues do whatever work was necessary to obtain expression in mammalian cells?

A. That's correct, yes.

Q. Did you leave up to the judgment of Dr. Browne and his associates how to accomplish that result?

A. Could you repeat the question again?

Q. Yeah. Did you rely on Dr. Browne and his colleagues for selecting the way to achieve that result?

A. 'That result' means expression?

Q. Expression in the mammalian host cell system.

A. Mostly, yes.

212. Dr. Lin's testimony at page 209 reads as follows:

Q. So it was Dr. Browne and his colleagues who selected the vector for transfecting or transforming the cells; is that correct?

MR. SCOTT: Calling for hearsay of our witness.

THE WITNESS: Could you repeat the question.

BY MR. RICHTER:

Q. Let me rephrase the question in light of your counsel's objection. It was not you who selected the vector for transforming or transfecting the cells; is that correct?

A. That's correct, yes.

Q. You didn't design that vector?

A. No.

Q. And you didn't make it?

A. No.

213. Dr. Lin's testimony at pages 209-10 reads as follows:

Q. Did you give Dr. Browne any specific instructions as to the culture medium that should be used to grow the cells?

A. No.

214. Thus, in my opinion, the expression of recombinant human EPO would be obvious to one skilled in the art at the time, once the gene sequence for EPO was known, since

Dr. Lin, who is the sole named inventor on each of the patents in suit '868, '933, '422, '698, and '080 provided no instructions for expressing EPO within a mammalian cell line to either Dr. Browne or Ralph Smalling including the vectors and culture medium. (*See also* Lin Testimony cited *supra* in paragraphs 99-102). Therefore, Dr. Browne and Mr. Smalling must have relied solely upon the techniques and operating conditions known to those of ordinary skill in the art for expressing the EPO polypeptide in mammalian cells.

215. Based upon my review of Dr. Lin's deposition testimony of April 9, 1991 in the '097 and '334 Interferences, AM-ITC 00410931-00411088, I conclude that he was not involved in the purification process of EPO at Amgen and that he provided this task to a Dr. Thomas Strickland. Further, I conclude that he provided no other information to Dr. Strickland other than the known literature regarding purification of human EPO. I draw my conclusions from Dr. Lin's testimony at pages AM-ITC 00410960-61 that reads:

> THE WITNESS: I did not personally involve in the isolation of glycosolated polypeptide.
> BY MR. RICHTER: Who was personally involved in that effort?
>
> A. I believe Tom Strickland and his associates.
>
> Q. And it was Dr. Strickland who worked on the purification of erythropoietin at Amgen and his colleagues?
>
> A. Yes. Tom Strickland and his colleagues.
>
> Q. Did you assign that task to Dr. Strickland?
>
> A. Yes.
>
> Q. Did you give Dr. Strickland any specific instructions how to obtain purified erythropoietin?
>
> A. I think I gave him some of the literature regarding the purification of the erythropoietin.
>
> Q. I'm sorry, I didn't understand your answer.
>
> A. Some of the literature regarding the purification of urinary erythropoietin, if I remember correctly.
>
> Q. You gave him some literature?

A. Yeah, I believe so.

216. During the same deposition, Dr. Lin indicated that the purification technique mentioned within the specification of his November 30, 1984 patent application was developed by Dr. Lai. AM ITC 00410964 reads:

Q. I'd like to refer you first to page 64 of the application, which is part of example 10, and you find the paragraph which begins "mammalian cell expression" at line 16?

A. Yes, I do.

Q. And it reads, "Mammalian cell expression products may be readily recovered in substantially purified form from culture media using HPLC (C 4) employing an ethanol grading, preferably at p07." Did I read that correctly?

A. That's correct, yes.

Q. Now, the HPLC procedure, which is referred to there, is a reference, or is one attempt, to isolate recombinant EPO from a mammalian expression system; is that correct?

A. That's correct, yes.

Q. Is it true that the suggestion or the idea of using HPLC (C4) in an effort to isolate erythropoietin from a mammalian expression system culture medium was not your suggestion or idea?

A. No.

Q. That is correct?

A. That's correct, yes.

Q. And do you know whose suggestion or idea it was?

A. Now I remember. This probably was Por Lai?

Q. Por Lai?

A. Yeah. He was doing the protein sequencing at the time.

217. As I have previously stated, it is my opinion, that the purification of rHuEPO is obvious to one of ordinary skill in the art. The literature, in particular Miyake (1977), would enable someone of ordinary skill in the art to use the techniques described for purifying urinary EPO to purify recombinant human EPO without undue experimentation.