DECLARATION OF HARVEY F. LODISH, Ph.D. IN SUPPORT OF AMGEN INC.'S OPPOSITION TO ROCHE'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY FOR DOUBLE PATENTING OVER CLAIM 10 OF THE '016 PATENT

PART 2

each of the intended probes in equal proportions. This made the selection of appropriate hybridization conditions for any partially- or fully-degenerate set of oligonucleotide probes even more difficult and non-obvious in 1983.

62. In addition to the complexity of optimizing probe selection and hybridization conditions, one seeking to clone an unknown gene sequence would also confront the uncertainty whether the desired gene sequence was in fact present in the library being screened, and was present in a form that could be detected by the probes being used.

63. In the context of genomic DNA libraries, the amino acid sequence selected for targeting might cross an exon boundary — that is a genomic splice site — thus rendering the probe sequences deduced from the amino acid sequence useless in finding the genomic DNA sequence. Alternatively, the process of cutting the genomic DNA into manageable fragments may have sheared the targeted nucleotide sequence, again rendering the selected probes useless for cloning. Finally, the noise to signal ratio of unwanted to targeted DNA in a genomic library is extremely high, thus making increasing the likelihood of both false positives and false negatives.

64. In the context of cDNA libraries, the risks of failure were equally daunting. The first risk was whether the library in fact contained copies of the desired mRNA, and whether those copies were adequately represented in the library to detect by hybridization screening. If the cells or tissues used to construct the library did not in fact produce stable mRNA for the protein being sought, the screening would fail. Absent some empirical proof that mRNA encoding the desired protein was in fact present in the library, there could be no assurance that a cDNA library in fact contained a copy of the DNA being sought. Indeed, this is precisely what happened to Genetics Institute in 1983-84. GI had built and used a cDNA library from renal

tumor cells supplied by Dr. Sherwood to screen for DNA encoding EPO on the premise that Sherwood's cells exhibited erythropoietic activity in a bioassay. After Lin cloned the EPO gene from a genomic DNA library, GI repeated Lin's success, and then used the genomic clone to screen its cDNA library looking for EPO message. Only then did GI confirm that the cDNA library it had built from Sherwood's calls and relied upon to search for EPO DNA in fact did not contain EPO cDNA, presumably because Sherwood's renal tumor cells contained no measurable amount of EPO mRNA.

65. Creating a cDNA library that contained a full-length cDNA encoding human EPO was neither simple nor obvious in 1983. Finding suitable cells to use as a source of the desired human EPO mRNA for the cDNA library, appeared to be impossible in 1983. Even if one of ordinary skill in 1983 had been able to acquire a useful amount of mRNA encoding human EPO from a cellular source, generating a cDNA library containing full-length versions of cDNAs representing expressed proteins was difficult in 1983 (and still is today, even with advanced methods and materials). The enzyme used to create cDNAs from mRNA, called "reverse transcriptase," starts copying the mRNA from the 3' polyadenylated end of the mRNA. A "full-length" cDNA is obtained when the reverse transcriptase enzyme makes a DNA copy of the entire mRNA, including the 3' untranslated region ("UTR"), the full coding region (the region of the cDNA containing codons for the amino acids of the encoded protein), and the 5' UTR. Full-length cDNAs were often difficult to obtain because the reverse transcriptase enzyme frequently falls off before it completes copying the entire mRNA, thus producing a mixture of cDNAs of varying lengths corresponding to each mRNA present in the pool. Consequently, full-length cDNAs (*i.e.*, cDNAs containing the sequence encoding the complete protein, including particularly the N-terminus of the protein) would be proportionately under-represented in the

library. In 1983, if one isolated an incomplete cDNA clone encoding less than the complete desired protein, it took substantial work to isolate the full-length cDNA clone from the library (assuming that the library in fact contained a full-length clone) and to determine which cDNA if any encoded the entire protein.

66. In 1983 (as today) there was simply no predictable assurance of success. Thus, contrary to Roche's simplistic contentions, in 1983 (as today) the art and the genius of successful cloning lay in selecting, from among many possible alternative choices, an appropriate length of probe to use for DNA screening, an appropriate amino acid sequence to target with the probe(s), an appropriate set of hybridization conditions under which to perform the screening, and an appropriate library of DNA screens for use in probing. A very small mistake or misjudgment in any of those variables could result in abject failure, with little or no indication of what in fact caused the failure. Was it the hybridization conditions? Was it the probe length? Was it an error in the amino acid sequence being targeted? Or was it the fact that the library simply did not contain the DNA sequence being sought, either because it was not present, or it was only present in an incomplete or broken form different than the form encoded in the probe? Any or all of those reasons could explain the failure, and there was simply no way for the most highly skilled artisans, let alone those of ordinary skill, to predict in advance what set of choices would result in success.

67. Without Dr. Lin's patent disclosure in hand, one of ordinary skill would not have had a reasonable expectation that one would be able to create a cDNA library that actually contained a cDNA encoding human EPO, or that, even if such a clone existed in the library, one would be able to identify and isolate that cDNA clone. And because one of ordinary skill would not have had a reasonable expectation of success in obtaining a cDNA clone encoding EPO, it

could not have been obvious to use the "EPO cDNA clone" to "clone and characterize" the human EPO gene. After Dr. Lin's inventions, of course, everything changed.

D. A PERSON OF ORDINARY SKILL IN THE ART IN POSSESSION OF A DNA SEQUENCE ENCODING EPO IN 1983 WOULD STILL HAVE LACKED A REASONABLE EXPECTATION OF SUCCESS IN PRODUCING IN VIVO BIOLOGICALLY ACTIVE EPO OUTSIDE THE HUMAN BODY ABSENT PROOF OF SUCCESSFUL PRIOR PRODUCTION OF SUCH EPO

68. A central premise of Roche is that once Dr. Lin was in possession of a DNA sequence encoding EPO, he could predictably expect that he would produce *in vivo* biologically active EPO by merely inserting the DNA into mammalian cells using known techniques and waiting for production. I disagree.

69. While some of the tools and techniques for producing recombinant glycoproteins in mammalian cells were known prior to October 1983, the field had not progressed to a state in which one of ordinary skill in the art could reasonably expect success, particularly where the protein of interest (EPO) had never been successfully produced in a recombinant cell.[11] Moreover, in my opinion, a person of ordinary skill in the art at that time would have reasonably believed that it was just as likely that *in vivo* biologically active EPO could not be successfully produced. A person of ordinary skill in the art in October 1983 would have expected that differences in post-translational modifications like glycosylation between the cells in the human body that naturally produce EPO and the selected recombinant cells could prevent production of EPO glycoprotein in a form that was biologically active *in vivo* absent experimental validation.

70. The following facts are apparent from the literature published before (or, in some instances, contemporaneous with) Lin's inventions:

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[11] My opinion would be the same if the relevant date of analysis were prior to November 30, 1984.

- Erythropoietin is a glycoprotein and that at least the sialic acids attached to the carbohydrate chains are important for biological activity.
- Oligosaccharide chains added to proteins by eukaryotic cells, specifically including mammalian and other vertebrate cells, have an extremely large variety of different carbohydrate substituents, structures, and properties.
- Specific oligosaccharide structures are required for the function of many glycoproteins.
- The host cell species and cell type can determine the oligosaccharide structures attached to a particular glycoprotein.
- Mammalian cells perform many post-translational modifications in addition to glycosylation that impact function in a species and cell-type and protein specific manner. Whether EPO had any such modifications was unknown.
- At the time of Lin's inventions only a handful of recombinant glycoproteins had been expressed in vertebrate cells, and prior to November 1984 only one (tPA) may have been shown to have *in vivo* biological activity.
- It was assumed that recombinant proteins produced in host cells from the homologous cell types and species would be more likely to have *in vivo* biological activity and be useful than would recombinant proteins produced in cells of a different type or different species.
- Given the art of expression of recombinant proteins in mammalian cells in 1983 – 1984, there was no reasonable expectation that any given glycoprotein could be produced in any specific mammalian or other vertebrate host cell in an amount sufficient to have an *in vivo* biological or therapeutically effective activity.

71. In addition, the 1983-1984 time period was the very birth of the technology of recombinant expression of glycoproteins in mammalian cells. As I discussed above, even by the end of 1984, there was insufficient experience with this technology to draw any conclusions about whether any particular recombinant glycoprotein could be expressed in an *in vivo* biologically active form. Only a few proteins had been expressed, and in no case had reasonable

fidelity of glycosylation as compared to the native glycoprotein been established. Moreover, most of the earliest proteins produced did not require glycosylation to be biologically active *in vivo*, and in almost all instances, the researchers had not even tested whether their recombinant products had any *in vivo* biological activity.

72. Prior to Dr. Lin's successful expression of *in vivo* biologically active recombinant human EPO, there were few, if any, reports of glycoproteins that had been produced by recombinant means and demonstrated to possess *in vivo* biological activity. I understand that during prosecution of the patents-in-suit, Amgen's attorneys characterized EPO as an "obligate glycoprotein."

73. As discussed above, earlier experiments by Goldwasser and Dordal demonstrated that naturally occurring EPO that lacked sialic acids or was deglycosylated lacked in vivo biological activity. Therefore, a person skilled in the art in 1983 would have expected that EPO likely required some form of glycosylation in order to be *in vivo* biologically active.

74. Two implications followed from this expectation. First, it meant that some structure in addition to EPO's amino acid sequence was required and must be present on the protein in order for the protein to have *in vivo* biological activity. What those precise structures were for EPO and whether any recombinant cell would predictably produce such structures as were needed for EPO's *in vivo* biological activity was not known or obvious prior to Lin's work, although for EPO it evidently entailed some form of glycosylation. Whether differences in the type, amount, or structure of the required glycosylation would affect the protein's *in vivo* biological activity was not known, and what if anything else in addition to glycosylation might also be needed, was not known. Second, it was not known whether a recombinant cell would add other unwanted or unneeded structures to the protein, or change the protein in

some way that would impair biological activity *in vivo*. In sum, until a particular protein was actually expressed in a cultured cell and tested for bioactivity *in vivo*, it was not possible to predict with reasonable confidence whether the recombinantly produced glycoprotein would have the desired *in vivo* biological activity. Once Lin demonstrated that EPO could be produced in vertebrate cells, e.g., CHO and COS, and have in vivo bioactivity, efforts to produce recombinant EPO in other vertebrate cells became much more predictable.

75. These facts establish that at the time Lin's inventions were made, it was highly unpredictable whether EPO could be produced in an *in vivo* biologically active glycosylated form from recombinant host cells.

76. I understand that it is improper to use hindsight to determine whether a patent claim would have been obvious at the time of invention. In my opinion, Roche's argument that the successful outcome of Lin's plan to produce *in vivo* biologically active material in heterologous recombinant host cells was expected or predictable is an exercise in hindsight.

77. A priori, in 1983-84 an ordinarily skilled artisan would have had no way of knowing whether CHO host cells would add appropriate glycans to human EPO and, if it did, would add them efficiently enough to produce a population of EPO glycoproteins of sufficient quality to provide detectable *in vivo* biological activity. Thus, in 1984 there was no reason to believe that a transformed CHO cell would modify EPO with the same or similar sugars as a human cell that naturally makes EPO, or that the sugars added by the non-human cell would impart the claimed biological effect.

78. Today we know that CHO cells are a good host for the production of recombinant human glycoproteins. But in 1983, the field had no experience expression of glycoproteins on which to draw.

79. Post-1984 publications concerning the glycosylation of recombinant glycoproteins, including EPO, reinforce the surprising nature of Lin's successful expression of *in vivo* functional EPO from heterologous cells. For example, a 1991 review article emphasized that researchers were ***pleasantly surprised*** that when they examined the glycosylation of recombinant proteins expressed in CHO cells that the CHO oligosaccharides were as similar as they are to the native glycosylation of these human proteins:

> "Detailed *N*-linked and *O*-linked oligosaccharide structures have been determined for several glycoproteins produced using recombinant CHO cells, including EPO, t-PA, interferon-βl and IL-2. ***A pleasant surprise from these recent analyses*** has been the remarkable degree to which the oligosaccharide structures from the CHO-produced glycoproteins correspond to the structures of those same proteins isolated from human urine or produced using normal human diploid cells. As a result, Chinese hamster ovary cells have emerged as the cell line of first choice for the synthesis of recombinant human therapeutic glycoproteins, although CHO cells do possess deficiencies that may limit their applicability in specific cases, such as limited capability for γ-carboxylation and inability for oligosaccharide sulfation." Gooche *et al.*, "The Oligosaccharides Of Glycoproteins: Bioprocess Factors Affecting Oligosaccharide Structure And Their Effect On Glycoprotein Properties" *BioTechnology* 9:1347-1355 (1991) (emphasis added) (Exhibit X).

80. Similarly, a scientific 1988 publication analyzing the glycosylation patterns found on EPO states that "[t]his paper proved, ***for the first time***, that recombinant technique can produce glycoprotein hormone whose carbohydrate structures are common to the major sugar chains of the native one." Takeuchi, Makoto, *et al.* "Comparative Study of the Asparagine-linked Sugar Chains of Human Erythropoietins Purified from Urine and the Culture Medium of Recombinant Chinese Hamster Ovary Cells," *J. Biol. Chem.* 263(8):3657-3663 (1988) (emphasis added) (Exhibit K).

81. A 1993 review article by Lis and Sharon ("Protein glycosylation, structural and functional aspects," *Eur. J. Biochem.* 218:1-27 (1993) (Exhibit Y)) is particularly compelling evidence of the inventive significance of Dr. Lin's process and EPO product inventions.

> Also, genetic engineering makes it possible to produce glycoproteins in heterologous systems on a large scale, both for research purposes and for therapeutic use (Table 1). We are indeed witnessing the emergence of glycotechnology [70], a branch of biotechnology that uses novel approaches to manipulate carbohydrates or related materials, with the aim of creating new products or new procedures for the betterment of our lives. ***An impressive example is erythropoietin, a circulating glycoprotein hormone that stimulates erythropoiesis, which has the distinction of being the first recombinant glycoprotein produced industrially for clinical use.*** It is being employed on a wide scale for the treatment of anemia in patients on haemodialysis [71]; its sales in 1991 reached $645 million. Another clinically important recombinant glycoprotein is the thrombolytic agent, tissue plasminogen activator (tPA), with sales of close to $200 million in the same year. Still, ***the manifold effects of carbohydrates on the stability and biological activities of glycoproteins are a source of much concern in the biotechnological production of pharmacologically useful glycoproteins*** [72-75]. (emphasis added).

82. This passage from Lis and Sharon is significant in a number of respects. First, it acknowledges that "glycotechnology" was still an emerging field 10 years ***after*** Dr. Lin's inventions. This statement makes plain that the field of glycoprotein production was new and unpredictable in the 1983-84 timeperiod. Second, Lis and Sharon rightly describe Lin's work as "an impressive example" of glycotechnology, given that it "has the distinction of being the first recombinant glycoprotein produced industrially for clinical use." Lastly, the authors note that "the manifold effects of carbohydrates on the stability and biological activities of glycoproteins" remained "a source of much concern in the biotechnological production of pharmacologically useful glycoproteins."

83. Successful heterologous expression of *in vivo* biologically active EPO from recombinant host cells was unexpected and surprising. Thus the claimed production of *in vivo* biologically active EPO is not obvious in light of EPO DNA-containing cells. EPO was the one of the first two glycoproteins requiring glycosylation for *in vivo* function to be successfully produced by recombinant means in mammalian. Therefore, ordinarily skilled artisans would not have expected recombinant EPO produced in non-natural cell types and species to have proper *in vivo* biological function until after Dr. Lin's successful experiments.

84. Because of the uncertainties in the art I described above, in my opinion Dr. Lin could not have reasonably expected to have produced *in vivo* biologically active EPO until he actually received the positive *in vivo* test results. Thus, Dr. Lin did not have possession of the inventions of the claims-in-suit until he actually successfully transformed and tested heterologous mammalian cells for the production of *in vivo* biologically active EPO, which I understand to have occurred in early March 1984.[12]

85. Until Dr. Lin proved that *in vivo* biologically active EPO could be made in cells outside of the body, no one could predict whether it would ever work. Once Dr. Lin was successful, persons skilled in the art knew that EPO could be produced in an *in vivo* biologically form outside the body. Future efforts to produce EPO under different conditions might require some additional experimentation, but the expectation of success changed dramatically. By proving *in vivo* biologically active EPO could be produced in hamster cells and monkey cells in addition to the natural production from human cells in the body, Dr. Lin's teachings would have led one of ordinary skill in the art to believe that *in vivo* biologically active EPO could be

[12] *Amgen Inc. v. Chugai Pharm. Co. Ltd.*, 13 U.S.P.Q.2d 1737, 1748 (D. Mass. 1989).

expressed in a broad range of different vertebrate or mammalian host cells, albeit with some additional experimentation required.

E. DR. LIN'S PATENT APPLICATIONS DESCRIBE A SUCCESSION OF DIFFERENT INVENTIONS

86. To successfully produce *in vivo* biologically active recombinant EPO for the first time in history, in the midst of all the uncertainty described above, it was necessary to, among other things: (a) "clone" the EPO gene by discovering its DNA sequence, (b) discover and select cell types that could successfully produce biologically active EPO in sufficient quantities for administering to patients, (c) genetically engineer and modify such cells to express biologically active EPO, and (d) validate that the cells actually produced sufficient quantities of *in vivo* biologically active EPO. Each of these successive inventions was necessary to develop a protein that could be administered to patients to treat anemia. None of these inventions, standing alone, were sufficient to achieve that result.

87. In the 1983-84 time period, Amgen's Dr. Fu-Kuen Lin made a series of path-breaking inventions which he documented in a succession of four patent applications filed on December 13, 1983 (Ser. No. 561,024), February 2, 1984 (Ser. No. 582,185), September 28, 1984 (Ser. No. 655,841), and November 30, 1984 (Ser. No. 675,298). The later applications each build on the information that was included in the preceding applications. I find that the successive disclosures of these applications closely track the progression of Dr. Lin's experiments at Amgen, with only the early cloning information present in the first application, and the complete description of all of his inventions set forth in the fourth application. Thus, the successive patent applications illustrate the progression of Dr. Lin's work over time and highlight the fact that Dr. Lin made multiple, significant scientific discoveries, not a single scientific discovery.

88. Magistrate Judge Saris's factual findings regarding Amgen's inventions are found at pages 1746-1751 of her opinion in *Amgen Inc. v. Chugai Pharm. Co. Ltd.*, 13 U.S.P.Q.2d 1737 (D. Mass 1989). The Judge found that: (a) "[t]he successful cloning of the EPO gene took place in September or early October, 1983"; (b) "[o]n February 13 and 14, 1984, Amgen conducted experiments to show that the recombinant human EPO produced in the COS cell was biologically active" (I understand that these were *in vitro* tests); and (c) "[f]rom March 1-9, 1984, Amgen conducted an *in vivo* bioassay and determined that the recombinant EPO was biologically active." *Id.* at 1748.

89. The last of Dr. Lin's four applications, which I have been told is the effective specification document for all of the patents-in-suit, contains a breadth of information and teaching relating to EPO. For example, Amgen's Patents provide the following information:

- The precise full-length amino acid sequence of the human EPO polypeptide, including the signal peptide and C-terminal arginine residue, which are subsequently removed from the EPO polypeptide (*see* Figure 6 of Amgen's Patents);
- The precise sequence of the human EPO gene as it exists in the genome of human cells, including both the regulatory and structural regions of the gene (*see* Figure 6);
- The sequence, number and arrangement of exons and introns in the human EPO structural gene, including all of the EPO intron splice donor and splice acceptor sites;
- Methods for isolating the human EPO gene from a human genomic DNA library;
- Methods for making cells that produce human EPO;
- Methods for producing biologically active human EPO glycoprotein products in genetically manipulated vertebrate cells;
- Methods for amplifying EPO DNA within cells;
- Variants and analogs of EPO polypeptides and methods of making them;

- DNA sequences that encode human EPO, but differ from the natural EPO DNA sequences by including preferred codons for expression in prokaryotic and yeast cells;
- Demonstrations of immunological, *in vitro*, and *in vivo* biological properties of EPO produced by genetically manipulated cells; and
- Methods for treating anemic patients by EPO therapy.

90. Particularly as of 1983-84, the breadth and quality of Dr. Lin's experiments and the description of his methods and results were impressive, reflecting a series of truly breakthrough discoveries that garnered significant attention, respect, and acclaim when they were reported to the scientific community.

F. CLAIMS 3, 7-9, 11-12 AND 14 OF DR. LIN'S '933 PATENT WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART IN 1983-84, EVEN IN LIGHT OF '016 CLAIM 10

91. The differences between '016 claim 10 and '933 claims 3, 7-9, 11-12 and 14 are shown in the following chart:

'016 Claim 10	'933 Claims 3, 7-9, 11-12, 14
10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence: (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin; (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea; (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about	3. A non-naturally occurring erythropoietin glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. 7. The glycoprotein product according to claim 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell. 8. The glycoprotein product according to claim 7 wherein the non-human mammalian cell is a CHO cell. 9. A pharmaceutical composition comprising

4.3. (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0; (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin; (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and, (7) isolating erythropoietin-containing fractions of the eluent.	an effective amount a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier. 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient. 12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier. 14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

92. The asserted claims of the '933 patent are each significantly different than '016 claim 10 because they each depend on claim 3, and thus require: (1) a particular process of production of an erythropoietin glycoprotein, that (2) has a specific *in vivo* biological activity. Moreover, the dependent '933 asserted claims have further limitations that are not even suggested by '016 claim 10:

- '933 Claim 7: additionally requires that the EPO glycoprotein be produced in a non-human mammalian cell.
- '933 Claim 8: additionally requires that the EPO glycoprotein be produced in a CHO cell.
- '933 Claims 9 and 12: additionally require that the EPO glycoprotein be part of a pharmaceutical composition.

- '933 Claims 11 and 14: additionally require that the EPO glycoprotein pharmaceutical composition be effective in increasing the hematocrit of kidney dialysis patients.

93. Notwithstanding the significant differences between these claims, Roche contends that each of the '933 asserted claims would have been obvious to one of ordinary skill in the art in 1983 in light of '016 claim 10. Specifically, Roche contends that:

- "A 'glycoprotein product' would have been obvious in light of or inherent in 'recombinant erythropoietin' as used in claim 10 of the '016 patent." Roche Statement of Fact (Docket Item 492) ("RSF") 9;

- "Erythropoietin grown in a 'mammalian cell culture' as required by claim 10 of the '016 patent is a glycoprotein, and one skilled in the art in 1983 would have expected it to have 'the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells,' as called for in claim 3 of the '933 patent." RSF 9;

- "CHO cells were also well-known to those of skill in the art in 1983 as a preferred mammalian host cell culture for recombinant procedures in which biological activity was sought." RSF 10;

- "Limitations relating to the host cells, including the choice of the "specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells" and limitations relating to the host cell's ability to produce EPO at a greater rate cannot be considered patentable distinctions over the "mammalian cell culture" of claim 10 of the '016 patent." RSF 8;

- "[O]ne of ordinary skill in the art in 1983 would have understood that purified rEPO, such as claimed in claim 10 of the '016 patent, was intended for pharmaceutical use and it would be routine for one skilled in the art in 1983 to combine the rEPO with a diluent, adjuvant or carrier." RSF 12;

- Use of EPO "for treating kidney dialysis patients to increase a patient's hematocrit level [was] well known in the art in 1983." RSF 13;

- "One skilled in the art in 1983 would have known that rEPO, such as claimed in claim 10 of the '016 patent, could be converted into pharmaceuticals for treatment of a kidney dialysis patient by conventional and well-known means." RSF 6.

94. I disagree with Roche's argument. In my opinion, for the reasons explained in this declaration, each of the inventions as a whole claimed in the '933 asserted claims would not have been obvious to a person of ordinary skill in the art in 1983-84, even in light of '016 claim 10.

G. CLAIM 1 OF DR. LIN'S '422 PATENT WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART IN 1983-84, EVEN IN LIGHT OF '016 CLAIM 10

95. The differences between '016 claim 10 and '422 claim 1 are shown in the following chart:

'016 Claim 10	'422 Claim 1
10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence: (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin; (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea; (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3. (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0; (5) subjecting erythropoietin-containing eluent	1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin; (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and, (7) isolating erythropoietin-containing fractions of the eluent.	

96. Asserted claim 1 of the '422 patent is significantly different from '016 claim 10 because it requires a pharmaceutical composition comprised of a "therapeutically effective amount" of "human erythropoietin." The Court has construed to "therapeutically effective" to require certain in vivo effects. The Court has construed "human erythropoietin" to require a polypeptide having the amino acid sequence of naturally occurring human EPO, including urinary EPO. Nothing in '016 claim 10 requires a product containing the amino acid sequence of '422 claim 1, nor would anything in '016 claim 10 inform or instruct one skilled in the art what the amino acid sequence of naturally occurring EPO is or how to obtain a recombinant product that comprised it. Nothing in '016 claim 10 requires a "therapeutically effective" recombinant EPO, nor would anything in claim 10 inform or instruct one skilled in the art how to obtain such a product.

97. Notwithstanding the significant differences between these claims, Roche contends that claim 1 of the '422 patent would have been obvious to one of ordinary skill in the art in 1983 in light of '016 claim 10. Specifically, Roche contends that:

- "One of ordinary skill in 1983 would have understood that purified rEPO, such as claimed in claim 10 of the '016 patent, was intended for use in a *pharmaceutical composition,* in a *therapeutically effective amount.*" RSF 14;

- "It would be routine for one skilled in the art in 1983 to combine the rEPO with *a pharmaceutically acceptable diluent, adjuvant or carrier*." RSF 14.

98. I disagree with Roche's argument. In my opinion, for the reasons explained in this declaration, the invention as a whole claimed in claim 1 of the '422 patent would not have been obvious to a person of ordinary skill in the art in 1983-84, even in light of '016 claim 10.

H. CLAIM 7 OF DR. LIN'S '349 PATENT WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART IN 1983-84, EVEN IN LIGHT OF '016 CLAIM 10

99. The differences between '016 claim 10 and '349 claim 7 are shown in the following chart:

'016 Claim 10	'349 Claim 7
10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence: (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin; (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea; (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3. (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0; (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively	7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6. [4. Vertebrate cells which can be propagated *in vitro* which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.]

bind erythropoietin in said fluid to said resin; (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and, (7) isolating erythropoietin-containing fractions of the eluent.	

100. Asserted claim 7 of the '349 patent is significantly different from '016 claim 10 because it requires: (1) a particular process of production of the erythropoietin glycoprotein requiring host cells with specific genetic structures, and (2) that the erythropoietin glycoprotein be produced to certain high levels.

101. Notwithstanding the significant differences between these claims, Roche contends that claim 7 of the '349 patent would have been obvious to one of ordinary skill in the art in 1983 in light of '016 claim 10. Specifically, Roche contends that:

- "Limitations relating to the host cells, including the choice of the "specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells" and limitations relating to the host cell's ability to produce EPO at a greater rate cannot be considered patentable distinctions over the "mammalian cell culture" of claim 10 of the '016 patent." RSF 8;

- "because claim 7 fails to disclose or claim any method for making its rate of production possible, and also appears indefinite, its scope must be limited to what was enabled in the '349 patent, which shares the same specification as the Lin '008 patent, which was in turn incorporated into the '016 patent." RSF 21.

102. I disagree with Roche's argument. In my opinion, for the reasons explained in this declaration, the invention as a whole claimed in claim 7 of the '349 patent would not have been obvious to a person of ordinary skill in the art in 1983-84, even in light of '016 claim 10.

I. CLAIMS 1-2 OF DR. LIN'S '868 PATENT WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART IN 1983-84, EVEN IN LIGHT OF '016 CLAIM 10

103. The differences between '016 claim 10 and '868 claims 1 and 2 are shown in the following chart:

'016 Claim 10	'868 Claims 1 and 2
10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence: (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin; (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea; (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3. (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0; (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin; (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and, (7) isolating erythropoietin-containing fractions of the eluent.	1. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and (b) isolating said glycosylated erythropoietin polypeptide therefrom. 2. The process according to claim 1 wherein said host cells are CHO cells.

104. The asserted claims of the '868 patent are each significantly different from '016 claim 10 because each requires: (1) a particular process for production of the erythropoietin glycoprotein in a host cell with a specific structure, and (2) that the erythropoietin glycoprotein have a specific *in vivo* biological activity. Moreover, dependent claim 2 has the further limitation of production in a CHO cell that is not suggested by '016 claim 10.

105. Notwithstanding the significant differences between these claims, Roche contends that each of the '868 asserted claims would have been obvious to one of ordinary skill in the art in 1983 in light of '016 claim 10. Specifically, Roche contends that:

- "the rEPO of claim 10 of the '016 patent is *a glycosylated erythropoietin polypeptide* which inherently has the utility of the *in vivo biological property* that *increases production of reticulocytes and red blood cells.*" RSF 20;
- "It was routine in the art in 1983 when synthesizing recombinant proteins in mammalian cells to transform or transfect the cells with the isolated DNA sequence encoding the desired protein." RSF 20;
- "CHO cells were also well-known to those of skill in the art in 1983 as a preferred mammalian host cell culture for recombinant procedures in which biological activity was sought." RSF 20.

106. I disagree with Roche's argument. In my opinion, for the reasons explained in this declaration, each of the inventions as a whole claimed in the '868 asserted claims would not have been obvious to a person of ordinary skill in the art in 1983-84, even in light of '016 claim 10.

J. CLAIMS 4-9 OF DR. LIN'S '698 PATENT WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART IN 1983-84, EVEN IN LIGHT OF '016 CLAIM 10

107. The differences between '016 claim 10 and '698 claims 4-9 are shown in the following chart:

'016 Claim 10	'698 Claims 4-9
10. A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence: (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.0, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin; (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea; (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3. (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0; (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin; (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and, (7) isolating erythropoietin-containing fractions of the eluent.	4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and b) isolating said glycosylated erythropoietin polypeptide expressed by said cells. 5. The process of claim 4 wherein said promoter DNA is viral promoter DNA. 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and b) isolating said glycosylated erythropoietin polypeptide expressed by said cells. 7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA. 8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA. 9. The process according to claims 2, 4, and 6 wherein said cells are mammalian cells.

108. The asserted claims of the '698 patent are each significantly different from '016 claim 10 because they each require: (1) a particular process of production of the erythropoietin glycoprotein requiring vertebrate host cells with specific genetic structures (claim 4: an operatively linked non-EPO promoter, claim 6: amplified EPO DNA), and (2) that the erythropoietin glycoprotein have a specific *in vivo* biological activity. Moreover, the dependent claims have further limitations that are not suggested by '016 claim 10:

- '698 Claim 5: additionally requires that the promoter DNA be viral promoter DNA.
- '698 Claim 7: additionally requires that there be amplified marker DNA in the host cell.
- '698 Claim 8: additionally requires that the amplified marker DNA be the DHFR gene.
- '698 Claim 9: additionally requires that the host cells be mammalian host cells.

109. Notwithstanding the significant differences between these claims, Roche contends that each of the '698 asserted claims would have been obvious to one of ordinary skill in the art in 1983 in light of '016 claim 10. Specifically, Roche contends that:

- "The rEPO of claim 10 of the '016 patent is a *glycosylated erythropoietin polypeptide* which inherently has the *in vivo biological property* that *increases production of reticulocytes and red blood cells*." RSF 15;
- "The 'suitable nutrient conditions' and 'vertebrate cells' of claim 4 of the '698 patent are inherent in the '016 patent claim 10's mammalian cell culture of rEPO." RSF 15;
- "The 'promoter DNA, other than human erythropoietin promoter DNA' of claim 4 was routinely used in recombinant protein synthesis in 1983." RSF 15;
- "'DNA encoding the mature erythropoietin amino acid sequence of FIG. 6' would be produced by the process of claim 10 of the '016 patent in the mammalian cells." RSF 15;

- "Claim 4's step of 'isolating said glycosylated erythropoietin polypeptide expressed by said cells' corresponds to step 7 of the '016 patent claim 10." RSF 15;
- Viral promoter DNA "was a routine part of the synthesis of recombinant proteins in 1983." RSF 16;
- "Amplified DNA was routinely used in recombinant protein synthesis in 1983 and one skilled in the art in 1983 would have known to use the claim 10 process of the '016 patent to produce human EPO." RSF 17;
- "Both amplified marker gene DNA and DHFR gene DNA were routinely used techniques during synthesis of recombinant proteins in 1983 and thus would have been obvious to one skilled in the art in light of claim 10 of the '016 patent." RSF 18;
- Mammalian cells "[are] an explicitly covered element of the '016 patent claim 10." RSF 19.

110. I disagree with Roche's argument. In my opinion, for the reasons explained in this declaration, each of the inventions as a whole claimed in the '698 asserted claims would not have been obvious to a person of ordinary skill in the art in 1983-84, even in light of '016 claim 10.

II. MY OPINIONS IN THE *IN RE COLUMBIA UNIVERSITY PATENT LITIGATION* CASE ARE CONSISTENT WITH MY OPINIONS IN THIS CASE

111. The patents involved in the *In Re Columbia University Patent Litigation* case (Columbia case) contain claims that broadly encompass various aspects of cotransformation and coamplification and involve DNAs that encode proteinaceous material and glycoproteins.

112. One of my opinions in the Columbia case was that later claims that recite glycoproteins generally are obvious in view of the recital of particular glycoproteins in the earlier claims. A glycoprotein is simply a protein that has a least one sugar residue attached to it. As I explained in my Rebuttal Expert Report in the Columbia case none of the later claims requires that the glycoprotein be functional or therapeutically useful following administration to humans

or animals. None of the later claims requires that the protein be glycosylated in the same manner as in the donor species or that the cells reproduce any specific pattern of glycosylation. None requires any particular post-translational modification. None requires that the protein be "properly" modified following translation. All that is required is that the stated protein be a glycoprotein, *i.e.*, that it have at least one sugar attached to it.[13]

113. Roche contends that my opinions in the Columbia case support their argument that Lin's claimed inventions would have been obvious as of 1983. This is not true. In my Columbia report, I surveyed the state of the art as it related to certain subject matter at issue in the Columbia case. I did not attempt to survey or characterize the complete state of the art, nor did I address the complex choices and uncertainties that would have confronted one, such as Lin, who wished to produce a specific human glycoprotein having a specific *in vivo* biological function.

114. In Columbia, the issue was whether previously issued claims to production of proteins in CHO cells rendered obvious subsequently issued claims to production of glycoproteins in CHO cells. In Columbia, the only difference between the earlier claims and the later claims was a distinction between proteins and ***glyco***proteins, without any regard to whether the glycoproteins needed to be functional. Mammalian cells, such as CHO cells, were known to glycosylate certain proteins they produced. To one skilled in the art at the time, the production of a protein in CHO cells would have implied the production of a glycosylated protein, and thus a later claim to production of ***glyco***proteins in CHO cells added nothing significantly different than the earlier claim to production of proteins in CHO cells. Since the later claim to glycoproteins did not specify a particular carbohydrate structure, or any functional difference

[13] *See* Exhibit Z, Rebuttal Expert Report of Harvey F. Lodish, Ph.D. (Sept. 17, 2004) at ¶ 17.

between the earlier claimed proteins and the later claimed glycoproteins to distinguish themselves from the earlier protein claims, there was no patentable distinction between the earlier protein claim and the later glycoprotein claim. In other words, a skilled artisan would reasonably have predicted that the expression of a protein in CHO cells would produce a protein having at least some glycosylation, and that prediction would likely have proved to be true once the experiment was actually performed.

115. Here, however, the issue is very different. CHO cells do not normally produce erythropoietin, and before Lin's inventions, it was not known whether CHO cells could and would produce an erythropoietin glycoprotein that would perform the specific *in vivo* biological functions of human EPO: stimulating the production of red blood cells. Indeed, as detailed above and in my expert reports, there were then many reasons for skilled artisans to doubt whether recombinant CHO cells growing in culture could produce a glycoprotein product that performed the *in vivo* function of human EPO. The fact that a cell type, such as CHO, can glycosylate a protein it produces, does not mean that the glycosylated protein it produces will have the specific glycosylation and other post translational modifications that EPO requires in order to perform its specific biological function *in vivo*. Before Lin's inventions, in 1983-84, a skilled artisan would not have reasonably expected that the expression of an EPO protein in CHO cells grown in culture would successfully produce a glycoprotein that performed the biological function of human EPO *in vivo*. Until the experiment was actually performed, and empirical proof obtained to show that the product produced and isolated from CHO cells grown in culture actually performed the biological function of EPO *in vivo*, the most that a skilled artisan would have said at the time was they hoped it would do so.

116. Roche contends that portions of my expert report in the Columbia case confirm that the following techniques used in the field were obvious and well known:

- Transformation of mammalian cells with exogenous DNA
- The use of CHO cells for producing recombinant proteins
- The amplification of genes in mammalian cell cultures
- The use of dihydrofolate reductase (DHFR)
- The use of viral promoters

117. The fact that various techniques were known and practiced in the art hardly means that Lin's particular combination of techniques to solve several long-standing and highly challenging problems that others repeatedly tried but failed to solve would have been obvious. The notion is akin to the argument that a Monet painting would have been obvious because others before Monet had used paint brushes, paint, and canvas to paint water lilies.

It is true that workers of ordinary skill in the art had various types of cultured cells that could be used as host cells in transformation experiments and that CHO cells were among the different cell types that could be used as host cells for DNA transformation and recombinant protein production. It was also known that amplified genes could be selected by exposing cells to selection pressure and that the dihydrofolate reductase (DHFR) gene was one of several approaches that could have been used as an amplifiable selectable phenotype. Exogenous promoters, including viral promoters, were known to function in many types of cultured mammalian cells. My opinion that these techniques could be used to express recombinant proteins generally is consistent with my opinions in this case.

118. The fact that various types of cultured cells could be used as host cells in transformation experiments does not eliminate the very important difference between cells

transformed or transfected with an isolated DNA sequence encoding human erythropoietin and claim 10 of the '016 patent for a process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid.

119. Similarly, the fact that CHO cells could be used as host cells for DNA transformation and recombinant protein production does not eliminate the very important difference between the use of CHO cells transformed with a DNA encoding human erythropoietin in a process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and claim 10 of the '016 patent for a process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid.

120. The fact that amplified genes could be selected by exposing cells to selection pressure does not eliminate the important difference between using amplified DNA encoding human EPO in a process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and claim 10 of the '016 patent for a process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid.

121. The fact that the dihydrofolate reductase (DHFR) gene could have been used as an amplifiable selectable phenotype does not eliminate the important distinction between using the DHFR gene in a process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and claim 10 of the '016 patent for a process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid.

122. The fact that viral promoters were known to function in many types of mammalian cells does not eliminate the distinction between using promoter DNA, other than human erythropoietin promoter DNA, in a process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and claim 10 of the '016 patent for a process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid.

123. In this case, it is the novel and inventive way in which Lin combined and used these techniques — techniques that could be used in any number of ways by different artisans for different purposes — that provides the significant difference between the claims-in-suit and claim 10 of the '016 patent. In my opinion, nothing in claim 10 of the '016 patent suggests Lin's claimed use and application of these techniques as claimed in the Lin claims-in-suit.

124. I declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001).

Executed this 27th day of June, 2007.

/s/ Harvey F. Lodish, Ph.D.

HARVEY F. LODISH, PH.D.