EXHIBIT 24

United States District Court
District Of Massachusetts

****Confidential Pursuant To Section 5(c) of the Amended Protective Order****

Deposition

Of

Arnold Joel Berk, M.D.

(Exhibits Have Been Bound Separately)

June 7, 2007

Amgen, Inc.

v.

F. Hoffmann-La Roche, LTD

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UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

Certified Copy

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	Civil Action
	)	
F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company, and HOFFMANN-LA ROCHE, INC., a New Jersey Corporation	)	No. 05-12237 WGY
	)	
	)	CONFIDENTIAL
	)	
Defendants.	)	
	)	

Deposition of ARNOLD J. BERK, M.D., at 2151 Avenue of the Stars, Chateau IX, Los Angeles, California, 90067, commencing at 9:23 A.M., Thursday, June 7, 2007, before Judith Schlussel, CSR No. 4307.

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(This transcript contains material designated "Confidential" in accordance with the protective order in this case. Where applicable portions of testimony designated otherwise will be clearly marked with a parenthetical. Please treat any such segments of designated testimony in accordance with the protective order.)

document and tell me if you recognize it.

A. Well, I recognize that it's minutes from a scientific advisory board meeting, but I -- either I didn't receive these kinds of minutes myself or I didn't pay much attention to them, because I don't recall seeing minutes like this before. 12:10:06

Q. Now, on the second page of this document, which ends in the Bates No. 829, there's a heading that says "project summaries" and then one of the entries there is Vector Task Force. Do you see that? 12:10:28

A. Yes. Uh-huh.

Q. Your name is there, or there is Arnie Berk next to that. Is that you? 12:10:36

A. Yes.

Q. What was the Vector Task Force?

A. That was a group that worked on developing vectors for expressing proteins at high levels in different cell types. 12:10:55

Q. And were you involved in developing vectors in -- actually, the date of this document, if you look at it, is June 16 through 17, 1981. Do you see that?

A. Yes. 12:11:11

Q. Were you involved in developing vectors to

be used in mammalian host cell expression in this time frame for Amgen?

A. Yes.

Q. Did you have personal involvement in it or were you simply advising as a member of the Scientific Advisory Board? 12:11:25

A. Well, I met with the group, the small group at Amgen that was working on the development of these mammalian cell expression vectors. I met with them fairly regularly. We discussed how to proceed. But I didn't do the experiments with my own hands. 12:11:42

Q. On Bates page ending in 836 under the bottom of the page there's an entry, erythropoietin project leader, Gene Goldwasser. Do you see that? 12:12:13

A. Yes.

Q. Do you know why Dr. Goldwasser was the project leader for the erythropoietin project?

A. Yes. He was one of the world's experts, if not the expert, on human erythropoietin. 12:12:26

Q. And were you involved in this time frame with the erythropoietin project?

A. Well, as of this date, and I have to check my dates, I don't -- right. So I mean as of this date, the clone for EPO hadn't been obtained yet, 12:12:50 but there was a goal of obtaining and expressing

human erythropoietin from the very beginning of the founding of the company that was one of our most important, well, goals.

Q. And -- 12:13:10

A. One of our most important targets.

Q. And what vectors were being considered to express erythropoietin?

A. Plasmid vectors using transcription control regions from SV40 and polyoma, and we were 12:13:32 considering using adenovirus vectors.

Q. Would that include SV40 vectors?

A. No.

Q. Were you considering SV40 vectors?

A. Well, again, we used sequences from SV40 12:13:49 that are often referred to as SV40 vectors. But when I say adenovirus vector, I mean that we actually constructed a virus particle that has a new gene in it for erythropoietin that will infect cells the way adenovirus normally infects cells and 12:14:06 express the genes encoded in the viral DNA.

Q. You said that the goal of obtaining expressing human erythropoietin from the very beginning of the founding of the company was one of the most important goals, correct? 12:14:25

A. Yes.

Q. And why was that?

A. Well, it was recognized that erythropoietin would be a very good target for a beginning biotechnology company, because it would be useful for the treatment of patients with renal dialysis -- with renal failure who are seen by a specialized group of physicians, renologists, and they're treated regularly at dialysis centers, so that it would be a relatively -- it would probably be a very useful therapeutic agent for such patients. There was a large number of them and there was a, as I said, this relatively small group of physicians taking care of them that could be reached with a small sales force. So it was recognized to be a, have many advantages as an initial target for a beginning company. 12:14:37 12:15:01 12:15:28

Q. And when did it actually become a project at the company?

A. From the very beginning. I mean Fu Kuen Lin was working on trying to clone the EPO gene from the time that he was first hired, as far as I know. That was one of his important projects. And certainly, there were discussions at the Scientific Advisory Board meetings of strategies to take to clone the EPO gene from the very first meetings. 12:15:49 12:16:08

Q. Were there discussions at the Scientific Advisory Board about concerns as to whether the cloned gene for erythropoietin would have proper glycosylation when produced in mammalian cells? 12:16:27

A. Yes.

Q. And when do you first recall those discussions?

A. From the very beginning.

Q. Were there any other mammalian proteins that were under consideration to be cloned at that time period? 12:16:38

A. Yes.

Q. What were those mammalian proteins?

A. Well, some would be the interferons. At that time, I think -- mammalian proteins. I mean we were always trying to think of important new potential products. 1983 was pretty early, and so I remember that there was a distinct list of products, but Amgen became the highest -- EPO became the highest priority quite quickly. I don't recall. 12:16:58 12:17:30

Q. You mentioned interferons. Are those also glycoproteins?

A. Interferon beta and interferon gamma, I think, are glycoproteins. 12:17:48

Q. Was there also a concern at the time, this

would be prior to 1983, as to whether the interferon beta or interferon gamma would be properly glycosylated when produced in mammalian cells?

A. Well, there was information that the interferons were active when expressed in E.coli and not glycosylated, expressed in E.coli and re-folded in vitro and that they had interferon activity. 12:18:08

Q. So based on the expression of interferon in E.coli and the activity of that protein, did you have an expectation that interferon expressed in mammalian cells would also be active? 12:18:44

A. There was concern about whether any glycoprotein expressed in mammalian cells would be active, particularly because of the problem of having terminal sialic acid residues on all the carbohydrates. So you could have a situation where a non-glycosylated protein was biologically active in vivo, but the improperly glycosylated form of that protein which didn't have terminal sialic acids would be inactive, and that's what our concern was. 12:19:07 12:19:26

Q. So that concern about proper activity of -- strike that.

So prior to 1983, Amgen had concerns about whether or not interferon, alpha or beta, expressed in mammalian cells would have biological activity, 12:19:46

correct?

MS. FISHMAN: Objection; calls for speculation. You can answer.

THE WITNESS: Yeah. I'm not certain. I wasn't very involved in the work on the interferons. I was more involved in the work on erythropoietin. 12:19:58

Q. BY MS. CARSON: Do you recall discussions at the Scientific Advisory Board about concerns as to whether or not interferon expressed in mammalian cells would have biological activity prior to 1983? 12:20:15

A. Yes.

Q. So based on your own experience, Amgen did have that concern about interferon, whether or not it would be biologically active when expressed in mammalian cells prior to 1983? 12:20:34

MS. FISHMAN: Just one second. Same objection. But you can answer.

THE WITNESS: So by now I'm not quite certain of what the question is. 12:20:59

MS. FISHMAN: Here.

THE WITNESS: All right. According to, you know, my recollection, I don't recall specific discussions about the activity of the interferon specifically, but I do, but there was very much concern about the activities of glycoproteins in 12:21:24

general.

Q. BY MS. CARSON: And at the time it was recognized that interferon was a glycoprotein, correct? 12:21:41

A. Some of the interferons.

Q. It was also recognized that erythropoietin was a glycoprotein?

A. Yes.

Q. I'm going to ask the reporter to mark as 12:22:22 Berk Exhibit 10 a document bearing Bates stamp numbers AM-ITC 00064700.

(Deposition Exhibit No. 10 was marked for identification.)

Q. BY MS. CARSON: Dr. Berk, the reporter has 12:23:02 placed before you what's been marked as Berk Exhibit 10. Do you recognize this document?

A. I don't recognize this document.

Q. Can you just read through the letter to yourself, please. 12:23:18

A. Yes. All right.

Q. Do you recall recommending to anybody at Amgen that they obtain the COS-1 cell line from Dr. Yakov Gluzman at the Cold Spring Harbor Laboratory? 12:23:59

A. Yes.

Q. Can you tell me what you recall about that.
A. Yes. Again, I was directing this -- I was consulting in the area of mammalian cell expression, and I discussed with Jeff Brown, who wrote this letter, Dr. Jeff Brown, who was the person immediately under Fu Kuen Lin working on mammalian cell expression, and, at Amgen, and we discussed that it would be useful to have COS cells and that we wanted to obtain them. 12:24:15 12:24:39
Q. And why did you think that it would be -- the date of this document is November 11, 1981. So you had these discussions with Dr. Brown prior to November 1981; is that correct?
A. Yes. 12:24:53
Q. And why did you think it would be useful to have COS cells for use at Amgen?
A. Because they have this ability to replicate introduced plasmid vector DNA resulting in higher levels of the encoded protein expression than in many other cell lines. 12:25:18
Q. Now, you said that Jeff Brown was working with Dr. Lin. So Dr. Brown was working on EPO?
A. Yes.
Q. And were you recommending to Dr. Brown that he use COS cells to express cloned EPO in 1981? 12:25:34

A. That was one of the approaches that we were considering.

Q. And at the time that you suggested to Dr. Brown that he use COS cells to express EPO, did you have no expectation that COS cells could be used to express active, biologically active EPO? 12:25:52

A. Yes, I had reservations.

Q. Did you have no expectation that they would work? 12:26:05

A. I was very uncertain. I was very anxious to see the results of experiments to test its activity. I did not have certainty or even a reasonable expectation that the produced material would be biologically active. 12:26:25

Q. So you suggested to Dr. Brown to use the COS cells, but you didn't have a reasonable expectation that those cells could be used to express biologically active EPO, correct?

A. That's -- that's correct. 12:26:44

Q. Did you suggest any cell types to Dr. Brown that you thought would actually work?

MS. FISHMAN: Objection; mischaracterizes testimony. Lacks foundation. You can answer.

THE WITNESS: We didn't know whether, which cell line might work or might not work or whether 12:27:02

any cell line would work. This was a way of testing, using COS cells was a way of testing whether, was a way of producing the protein that would allow it to be tested. Before that we didn't know. 12:27:25

Q. BY MS. CARSON: The methods for testing the protein -- strike that. You said it would allow it to be tested. How would it be tested?

A. It would be initially tested for in vitro assays of erythropoietin activity and then subsequently in vivo assays. 12:27:41

Q. What in vitro assays are you talking about?

A. I would have to -- I don't recall the details of the in vitro assays. They involved treating cultured cells and looking at the response of cultured cells that are a good readout for what happens inside the body when there is a stimulation of red blood cell production. 12:27:58

Q. Were those in vitro assays well known at the time? 12:28:15

A. They were known to people studying erythropoietin. They were well described in the literature.

Q. What in vivo assays would have needed to be used to test the erythropoietin produced in COS 12:28:29

cells?

MS. FISHMAN: Objection; lacks foundation. You can answer.

THE WITNESS: An assay for red blood cell production inside a living animal. 12:28:40

Q. BY MS. CARSON: Were those in vivo assays well known among those that were working in the field at the time?

A. Yes. 12:28:53

Q. Were those in vivo assays being performed by laboratory technicians?

A. At Amgen are you asking or --

Q. In anybody's laboratory?

A. Yes. They could probably be performed by laboratory technicians. 12:29:07

Q. Now, you had suggested COS cells to Dr. Brown for use to express human erythropoietin, correct?

A. Yes. 12:29:31

Q. And do you recall what other cell types you suggested?

A. I suggested 293 cells and potentially HeLa cells.

Q. Has Amgen ever expressed, to your knowledge, EPO in 293 cells? 12:30:19

A. Yes.
Q. Those are human cells?
A. Yes.
Q. And was the -- when was that? 12:30:31
A. It was in this same time frame, early -- late 1983, early 1984.
Q. Now, based on -- did it happen after they expressed the protein in COS cells?
A. It was in the same time frame. I'm not 12:30:48 certain.
Q. So up until -- is it your opinion that up until the time that Amgen expressed human erythropoietin in 293 cells, there was no reasonable expectation that a biologically active in vivo 12:31:08 protein would be produced?
MS. FISHMAN: Objection; mischaracterizes testimony. Lacks foundation.
THE WITNESS: Again, there was concern that there -- that there might well be specific 12:31:26 glycosylation structures required for EPO in vivo biological activity that would be put onto the protein only in the very rare cells that produce erythropoietin at a very low level, and that production of erythropoietin in other cells we 12:31:46 expected would give us different kinds of

glycosylation and there was concern that that would, that might affect biological activity and also again the concern as to whether we would exceed the capacity of the cell to glycosylate proteins with high levels of expression. 12:32:07

Q. Prior to 1983, was it known what cell types were -- prior to 1983, was it known what cell types in the human body produced EPO?

A. It was -- there was evidence that EPO was produced in the kidney, but which cell type in the kidney was not clear. 12:32:26

Q. Now, did you suggest any kidney cells grown in culture to be used to express the clone to human erythropoietin? 12:32:47

A. 293 cells were derived from kidneys, human fetal kidney cells.

Q. And it's your opinion even for human 293 kidney cells prior to 1983, there was no expectation that you would be able to produce cloned human erythropoietin in those cells that was properly glycosylated and would have in vivo biological activity? 12:33:15

MS. FISHMAN: Objection; misstates testimony. Lacks foundation. But you can answer. 12:33:31

THE WITNESS: There was concern about

whether the glycosylation would be correct in 293 cells. There are many cell types in the kidney, and it wasn't determined until rather recently just which type of cell in the kidney was, the 293 cell was derived from. In fact, now we know it was derived from a neuronal cell. 12:33:53

Q. In your view, prior to 1983, what were the likely candidates of cells to attempt to express recombinant human erythropoietin? 12:34:13

A. Various mammalian cell lines. I mean --.

Q. And those various mammalian cell lines include the cell lines that we've been discussing, correct?

A. And many others. 12:34:37

Q. Would also include CHO cells?

A. Yes.

Q. And would also include COS cells?

A. Yes.

Q. Out of those various cell lines, were there any specific cells that were commonly being used by scientists in the laboratory to express cloned recombinant mammalian proteins? 12:34:51

A. Well, this was the beginning of that period and COS cells were used; 293 cells were also used. 12:35:13

Q. What about CHO cells?

A. They weren't, you know, used nearly as widely as COS cells or 293 cells because the COS cells and 293 cells have the advantage of working with the transient transfection assays, short term, easily done; obtaining CHO cells that express high levels of a protein is a much longer process and more difficult, and so it wasn't done as often. And I don't know, I can't think right now back in 1983 if I knew of any proteins that were being produced in CHO cells. 12:35:39 12:36:00

Q. Now, at the time, prior to 1983, the dhfr minus CHO cells were available, correct?

A. Yes.

Q. And the concept of co-amplification was also known prior to 1983? 12:36:15

A. Yes.

Q. Now, the COS cells that -- strike that. Do you recall suggesting the use of CHO cells for expression of recombinant human erythropoietin to Dr. Lin? 12:37:03

A. My recollection is that it was Bob Schimkie who first made that suggestion at the Scientific Advisory Board meetings and I agreed with that suggestion. 12:37:16

Q. And why did Bob Schimkie suggest the use of

CHO cells to Dr. Lin?

MS. FISHMAN: Objection; calls for speculation.

THE WITNESS: Well, I can't say what Robert Schimkie was thinking, but his lab is the lab that discovered the phenomenon of gene amplification and specifically in CHO cells with amplified -- with amplification of the dhfr gene and exogenously introduced dhfr gene. And it was students from his, post-docs and graduate students from his laboratory that were the ones that made the first applications to co-amplification of a co-integrated gene and the result in higher levels of expression. So he was very familiar with that work. 12:37:34 12:37:57 12:38:14

Q. You said that you agreed with his recommendation. Why was that?

A. Because it was another possible mammalian cell to try, and the plan was to experiment with several to find the best production system. 12:38:38

Q. And that, your agreement that CHO cells would be another possible mammalian cell line to try, that was prior to 1983, right?

A. Yes.

Q. And at the time that you agreed, did you have no expectation that biologically active human 12:39:00

EPO could be produced in CHO cells with in vivo biological activity?

A. Well, I hoped that we would be able to find some mammalian cell line that would allow us to produce in vivo biologically active erythropoietin. 12:39:21

Q. Did you have any reasonable expectation that it would allow you to produce in vivo biologically active erythropoietin?

A. No. We didn't know. We simply didn't know, so we didn't have a reasonable expectation and we were very concerned that the material that was produced in cultured mammalian cells would be, would not be biologically active in vivo or in vitro. 12:39:36

Q. So at this time, did you have a reasonable expectation that in vivo biologically active EPO could be made in any cell type? 12:39:55

A. No. We did not have a reasonable expectation. It was being tried for the first time and so we didn't know, particularly because of the very high level of glycosylation in erythropoietin. 12:40:14

Q. And based on that knowledge of the high level of glycosylation in erythropoietin, did you expect that you would be better off expressing in a mammalian cell line? 12:40:38

MS. FISHMAN: Objection; vague and

ambiguous.

THE WITNESS: Well, we were attempting expression in mammalian cells because that was the best opportunity to have proper glycosylation of the protein, and we had evidence that glycosylation would be important. 12:40:53

Q. BY MS. CARSON: And the evidence that glycosylation would be important, what evidence was that? 12:41:14

A. Well, that was this earlier work from the Goldwasser's laboratory that showed that removal of the carbohydrates eliminated in vivo biological activity.

Q. Were you involved in designing the probe sequences that were used by Dr. Lin to clone the erythropoietin gene? 12:41:45

A. You know, I was involved. I participated. I think that the sequences that he chose were not the precise sequences that I had suggested, but the same general area. I mean when we first got the amino acid sequence, I sat down myself and determined the number of different nucleic acid sequence that could encode that protein and proposed a scheme for synthesizing a mixture that would include all of those. 12:42:06 12:42:30

But that was a relatively obvious thing to do, so other scientists at Amgen did the same thing, including scientists that had more experience with the chemistry of the synthesis of the DNA so that they may have come up with a better scheme. 12:42:44

Q. And was that the scheme that succeeded in cloning the erythropoietin gene?

A. Yes.

MS. FISHMAN: Objection; vague and ambiguous. You've got to let me interpose my objection. 12:42:58

THE WITNESS: Sorry.

Q. BY MS. CARSON: Is that a yes?

A. The question was, were those sequences the ones that were used to clone the EPO gene? 12:43:11

Q. No. Was that scheme that you just referred to the approach that was used to ultimately clone the gene by Dr. Lin?

A. The approach of using a large mixture of different synthetic oligonucleotides that could encode the determined amino acid sequence from a short portion of erythropoietin was the approach that succeeded. And that was the first time that there was success in using a very large number of, a mixture of probes with a large number of individual 12:43:26 12:43:54

sequences.

Q. Now, were you personally involved in any of the experiments to clone the erythropoietin gene?

A. Yes. I mean I was involved in advising on approaches to clone the gene. 12:44:15

Q. Did you oversee any of the experimental work that went into cloning the erythropoietin gene?

A. I heard about the work as Dr. Fu Kuen Lin was doing it. I remember that I was the one who suggested that one could screen through potential clones by using oligonucleotides directed against a second set of amino acid sequences from the protein, and that approach was used. 12:44:28

Q. Did you ever consider as to whether or not you should be an inventor on the Lin patents? 12:44:52

A. No.

Q. And why not?

A. Because Lin did the work, did the, you know -- he was the one who did it. 12:45:26

Q. I'm going to ask the reporter to mark as Berk Exhibit 11 a document bearing Bates stamp Nos. AM-ITC 00138784 through 00138790.

(Deposition Exhibit No. 11 was marked for identification.) 12:46:10

Q. BY MS. CARSON: Dr. Berk, the reporter has

placed before you what's been marked as Berk Exhibit 11. Can you tell me if you recognize this document.

A. Again, I don't remember seeing notes of Scientific Advisory Board meetings. I may have done so, but I don't recall now. But I do recall the meetings. 12:46:25

Q. Now, this is a meeting from January 1982. Correct?

A. Yes. January 16, 1982. 12:46:48

Q. Actually, I'm confused by this document because then underneath it, it says February 27 through 28, scientific advisory board meeting. It's the next one. Okay. I got it.

So this meeting happened in January of '81? 12:47:06

A. Yes.

Q. Under current Amgen project activity, the first project listed is erythropoietin. Do you see that?

A. Yes. 12:47:16

Q. And there is mention of a team consisting of Japanese scientists and somebody by the name of Fisher at Tulane working together on a human tumor cell line which may produce EPO. Do you see that?

A. Yes. 12:47:30

Q. Do you recall who Dr. Fisher at Tulane was?

A. No.

Q. Were you aware of efforts to clone EPO from cDNA produced from mRNA in a tumor cell line?

A. Yes. 12:47:49

Q. What did you know about those efforts?

A. I knew that there was an effort to identify a cell that produced erythropoietin at a level high enough to make it possible to clone a cDNA.

Q. What would have been considered high enough to make it possible to clone a cDNA? 12:48:08

A. If one succeeded in cloning a cDNA. But the more messenger RNA you have to start with, the easier it is.

Q. And do you recall if any cell lines producing sufficient quantities of EPO mRNA were found in this time frame? 12:48:23

A. I do not recall that any were found, at least any were found that were available to Amgen.

Q. Now, you refer in your expert report -- 12:49:04

MS. FISHMAN: Are you done with this document?

MS. CARSON: For the time being, yes. Give me a minute. I'm finding where you refer to it.

Q. BY MS. CARSON: You refer in your expert report to -- and I'm looking at Page 30. 12:50:22

MS. FISHMAN: Which exhibit?

MS. CARSON: This is Exhibit No. -- your expert report has been marked as Berk 2, I believe.

MS. FISHMAN: The responsive or the initial expert report. 12:50:43

MS. CARSON: The first one is the responsive one. I think the second one is the actual expert report.

THE WITNESS: Right. That's Exhibit 8. 12:50:51

Q. BY MS. CARSON: Exhibit 8 is the expert report, thank you. I'm looking on page, it starts at, actually, Page 34. And you talk about, starting at the bottom of Page 23 -- I mean bottom of Page 33, "before Dr. Lin's discovery, Genetics Institute pursued multiple expression systems in parallel in order to produce an in vivo biologically active recombinant EPO." 12:51:31

The information that's provided in your report about Genetics Institute, did you have personal knowledge of Genetics Institute's efforts to clone EPO in the 1983-1984 time frame? 12:51:48

A. I had heard that the Genetics Institute and several other biotechnology companies were working on trying to clone EPO. 12:52:10

Q. And that was in 1983-1984?

A. Yes. We knew that there were other companies that were working on it. Again, it was a very good target.

Q. There is a lot of detailed information about Genetics Institute and what they -- their efforts and what they were doing in your expert report that's been marked as Berk Exhibit 8. Is this based on personal knowledge of what Genetics Institute was doing that you had at the time in '83-'84? 12:52:26 12:52:44

MS. FISHMAN: Objection; vague and ambiguous as to "what."

Q. BY MS. CARSON: You're welcome to read through what you had to say and tell me if any of this is based on your own personal knowledge. 12:52:53

A. Most of this is based on knowledge I've obtained from reading materials that have been published by Genentech or patent documents submitted by Genentech considerably after this period. 12:53:17

Q. So this information wasn't based on your recollection of information that you knew in '83 or '84, correct?

A. No. I was presenting this information to point out that other groups also were uncertain about the best way to produce biologically active 12:53:34

erythropoietin as a demonstration that there was uncertainty as to how to achieve in vivo biologically active erythropoietin.

Q. Genetics Institute was also pursuing expression in mammalian cells, correct? 12:53:54

A. Yes.

Q. So is it your opinion that in 1983-1984 time frame, mammalian cell was not an obvious choice of cell line to use to express a cloned mammalian protein? 12:54:44

MS. FISHMAN: Objection; mischaracterizes testimony and lacks foundation. You can answer.

THE WITNESS: Well, it's my opinion that there was considerable question as to whether it would be possible to express a biologically active erythropoietin in any cultured cell. 12:54:59

Q. BY MS. CARSON: But that wasn't my question. My question was whether or not in the 1983-1984 period, time frame, whether it's your opinion that mammalian cells were not an obvious choice of host cell to use to express a cloned mammalian protein? 12:55:17

A. That they were not an obvious choice?

Q. Yes. 12:55:29

A. I would say it was a very reasonable choice

details of how the assay is performed. I depended on the experts who were doing the assays to tell me whether there was detectable activity.

Q. BY MS. CARSON: When you say you relied on the experts who were doing the assays to tell you whether there was detectable activity, what do you mean? 02:16:19

A. I mean Dr. Joan Egrie. I had reports from her directly or indirectly about the in vivo biological activity. 02:16:34

Q. So those were reports that indicated that Dr. Egrie had obtained biologically active in vivo erythropoietin, correct?

A. Yes. You know, except for instances where the material was not biologically active. For example, the erythropoietin that had been deglycosated in vitro. 02:16:52

Q. But in reviewing that material, did you obtain an understanding as to how small amount of active material could be detected by the Cotes assay? Let me rephrase that. In reviewing that material, did you obtain an understanding as to how low of an activity material could be detected in that Cotes assay? 02:17:13 02:17:33

A. I don't know the limitations of detection

in that assay.

Q. How can you conclude that one of skill in the art would not have any reasonable expectation of producing biologically active erythropoietin as measured by this assay if you don't know what the lower level of detection of the assay is? 02:17:47

MS. FISHMAN: Objection; mischaracterizes testimony. Lacks foundation. You can answer.

THE WITNESS: Okay. The concern was whether there would be abnormal glycosylation that would greatly diminish the biological activity of the erythropoietin. And so that was something that could be assayed by this in vivo activity. One could either say yes, one saw activity or if it was, if there was a lower activity, then the lowest level of detection that one did not detect activity. 02:18:02 02:18:23

Q. BY MS. CARSON: I understand that it's your testimony that the concern was that there would be abnormal glycosylation that would greatly diminish the biological activity. But my question is, was there expectation that there would be no biological activity of the material that was recombinantly-produced in the mammalian host cells? 02:18:39

A. Well, there was not the expectation that there would be no biological activity. We were 02:18:55

hoping that there would be biological activity. We simply didn't have any way of being able to predict in advance whether there would be biological activity. 02:19:10

Q. So you couldn't predict in advance whether there would be any biological activity whatsoever in this material that was expressed from mammalian host cells; is that correct?

MS. FISHMAN: Vague and ambiguous. Sorry. 02:19:28
Objection; vague and ambiguous. Do you mean in vivo biological activity?

MS. CARSON: In vivo biological activity is what we're talking about. Do you want me to rephrase? 02:19:41

THE WITNESS: Yeah. I mean there was an assay for in vivo biological activity that we could apply and we could see if a sample had no activity in that assay or a measurable level of activity in that assay. 02:19:53

Q. BY MS. CARSON: And my question is, is it your opinion that there was no expectation that there would be any measurable activity using that assay in recombinant erythropoietin produced in mammalian host cells? 02:20:14

A. And I answer again that it's not that we

had no expectation that we would produce protein with in vivo biological activity. We certainly hoped that we would detect in vivo biological activity, but there was no basis on which we could say with any reasonable certainty that we would expect biological activity and there were some reasons to believe that we would not. I mean the preponderance of evidence was that it wasn't going to be straightforward to obtain this activity in cultured mammalian cells, but that it might well take a great deal of experimentation to find the proper conditions to get in vivo biological activity. 02:20:35 02:20:54

Q. When you say "a great deal of experimentation," what type of experimentation are you referring to? 02:21:07

A. Experimenting with production in different cell lines and experimenting with the level of production. 02:21:23

Q. Now, you said that it's not that you had -- that one would have no expectation that protein with in vivo biological activity would be produced. So there was some expectation that protein with in vivo biological activity would be produced, correct? 02:21:47

A. Yes. We hoped that there would be. Yes.

Q. So there was some expectation that it would be produced, correct?

MS. FISHMAN: Objection; mischaracterizes testimony. You can answer. 02:21:58

THE WITNESS: Okay. Yes, there was some expectation. If there had been no expectation, then one wouldn't bother to do the experiment. It's work and expense.

Q. BY MS. CARSON: Now, you said experimenting 02:22:15 with production in different cell lines. What types of cell lines are you referring to?

A. Various kinds of cultured mammalian cells and not necessarily only cell lines.

Q. And you also referred to experimenting with 02:22:46 the level of production. What are you referring to there?

A. Well, this gets to the concern that very high level expression might overtax the capacity of the cell to glycosylate the proteins, so that if the 02:23:03 proteins were expressed at very high level, they wouldn't be properly glycosylated and wouldn't have in vivo biological activity, but if they had been expressed at lower level, then the same cells might be able to. That was the thinking at the time. 02:23:17

Q. The high level expression, what do you

consider to be high level expression?

MS. FISHMAN: Objection; asked and answered. You can answer.

THE WITNESS: Okay. Again, generally, when I consider production of a recombinant protein in any system, in any cell, I consider that I've gotten significant production when I can see a band of that protein on an SDS polyacrylamide gel stained with coomasie blue. So it's C-O-O-M-A-S-I-E, blue. 02:24:01

And there' my phone doing it's trick.

So generally, when you have about one percent of the level of protein in a single polypeptide chain, you can detect that as a band that stands out on the gel above the other proteins. 02:24:17 And so that's just a rough ballpark estimate of what I think of as high level expression.

Q. BY MS. CARSON: Now, if you could direct your attention, we had marked the whole series of Amgen's asserted patents in this case, starting with 02:24:42 Berk Exhibit 2 and that goes through Berk Exhibit 6. I think that we looked at the claims of the 349 patent which is Berk Exhibit 3 and you pointed out that those cells, those claims specify a particular expression level. Correct? 02:25:15

A. Expression level, yes, as measured by mass

much more less likely to be able to produce it in a particular cell line that you would name. After having made it in COS cells, at least one would know that it is possible to produce in vivo biological activity in cultured cells and so if it worked in COS cells, it might work in other cells. But one could not determine -- one could not predict whether it would work in other mammalian cells until trying it. I think that that's the case for virtually every cell line; even today, one would not know until one had tried it. 02:39:37 02:39:52

Q. This unpredictability that we've been talking about or lack of certainty all stem from the variation in the glycosylation on -- let me see if I can find the term that you used -- on distal saccharides? 02:40:30

MS. FISHMAN: Objection; lacks foundation. You can answer.

THE WITNESS: Well, we're concerned about effects of differences in the oligosaccharides and the polysaccharides attached to the erythropoietin produced in the non-hemologous cell line compared to the normal in vivo hemologous cell that the protein is produced in. We were concerned that those differences would affect biological activity. 02:40:44 02:41:10

Q. BY MS. CARSON: Now, in terms of the -- in terms of the core oligosaccharides, could you predict that those would likely be the same when the protein EPO was produced in COS cells versus CHO cells? 02:41:30

A. Yes, the core oligosaccharides are the same in all vertebrates, I believe, I think in all eukaryotes, but certainly in fungi and humans, the original high mannose sugar or carbohydrate structure that is added initially before it's modified is very similar among all organisms, I believe. But I'm not certain of that. It's certainly very similar among all vertebrates. 02:41:52

Q. Is there some term that's applied to describe that universal phenomenon of core oligosaccharides? Like there is the central dogma. Is there something that they use in glycobiology to describe that, the fact that the core oligosaccharides are conserved between vertebrate cells? 02:42:11 02:42:32

A. Yes. They're just referred to as the high mannose, and you know, initial core oligosaccharides that are transferred from a particular lipid carrier to the polypeptide chain, I think it's lipoic acid, but I'd have to double check that. But that basic 02:42:51

chemistry, that basic enzymology is the same in all eukaryotes.

Q. Is there any particular group of scientists who established that the basic enzymology of those core oligosaccharides was shared across vertebrate cells? 02:43:11

A. Yeah. What's his name, Kornfeld, Stuart Kornfeld at Washington University was one of the leaders in this area. 02:43:30

Q. Was Dr. Kornfeld on the Amgen Scientific Advisory Board?

A. No.

Q. So now to go back to what my original question was. It was recognized prior to 1983 that all vertebrate cells shared these core oligosaccharides, correct? 02:43:58

A. Yes.

Q. And so the unpredictability that you've referred to was based on whether or not the olygosaccharides, the sugars outside of the core olygosaccharides would have an impact, correct? 02:44:12

A. Well, whether the final structure of the complete glycoprotein would have a significant impact. They're not simply added onto the core high mannose oligosaccharide. Parts of that are removed 02:44:31

and then there are additions to it.

Q. I'm going to ask the reporter to mark as Berk Exhibit 13 a document bearing Bates stamp Nos. AM-ITC 00347087 through 00347275. 02:46:08

(Deposition Exhibit No. 13 was marked for identification.)

Q. BY MS. CARSON: Dr. Berk, the reporter has placed before you what's been marked as Berk Exhibit 13. This is a series of pages of documents produced 02:46:32 by Amgen in this litigation. And the first pages that are 087 through 093, actually, through 094, I believe that you referred to this in your expert report?

MS. FISHMAN: Document speaks for itself. 02:46:57 You can answer.

THE WITNESS: Are you waiting for an answer from me this time?

MS. FISHMAN: She is.

THE WITNESS: You're waiting for an answer? 02:47:12

Q. BY MS. CARSON: Yes.

A. I don't recall this specific table. So I'm not sure which -- I believe that I did refer in the report to some of these dates. But I don't recall seeing this particular table. 02:47:33

Q. If you could direct your attention to Bates

page 00347128 in this document.

A. 347128. All right.

Q. If you could read through the first paragraph of Page 128 to yourself. It's after the list of people who were in attendance at the meeting. 02:48:19

MS. FISHMAN: Can you lay a foundation for this document, this witness?

MS. CARSON: I ask him to read it first. 02:50:06

THE WITNESS: All right.

Q. BY MS. CARSON: Do you know what erythropoietin alpha is?

MS. FISHMAN: Objection. First of all, are you asking him about the document or are you asking him aside from the document? 02:50:14

Q. BY MS. CARSON: Dr. Berk, if you don't understand the question, please feel free to ask me.

MS. FISHMAN: Objection; document speaks for itself and you haven't laid a foundation this witness knows anything about this document. 02:50:25

Q. BY MS. CARSON: Do you know what erythropoietin alpha is?

A. Erythropoietin alpha and beta were two very closely-related forms of erythropoietin that could be isolated from the human urinary material. There 02:50:42

is only a single erythropoietin gene, so they must be due to different modifications of the single polypeptide.

Q. And prior to 1983-1984, were scientists aware of two forms of erythropoietin, alpha and beta? 02:51:12

MS. FISHMAN: Objection; calls for speculation. You can answer.

THE WITNESS: I don't know when the first reports of these two different forms that could be separated by SDS gels was made. 02:51:25

Q. BY MS. CARSON: Do you know whether or not erythropoietin -- do you know what the difference is between erythropoietin alpha and erythropoietin beta? 02:51:42

A. I don't know what the difference is. It's probably something that's been determined in greater detail subsequently. I think at the time the thinking was that it was due to differences in glycosylation. 02:51:56

Q. And was it known that both erythropoietin alpha and erythropoietin beta had biological activity in vivo?

MS. FISHMAN: Objection; lacks foundation. You can answer. 02:52:09

THE WITNESS: I don't know the answer.
Q. BY MS. CARSON: Now, if you could direct your attention to the EPO time line that's at the beginning of this document, it starts on Bates page ending in 087. 02:52:52
A. Yes.
Q. On page ending in 092 -- actually, it starts on page ending in 091.
A. Yes. 02:53:21
Q. There is an entry next to the last entry on that page that says "human erythropoietin expressed in COS cells." Do you see that?
A. Yes.
Q. If you could look at Berk Exhibit 1, the demonstrative that was attached. 02:53:49
A. Yes.
Q. Now, that is -- is that the date that corresponds to your entry on your time line at January 1984, EPO gene expressed in mammalian cells? 02:54:21
A. Again, what is the specific question?
Q. Well, in this time line document, okay, there is an entry that says January 10 through 17, 1984, human EPO expressed in COS cells using human genomic DNA and then it cites a series of support. 02:54:43
I'm asking you if that is the date that you're

referring to on your demonstrative that was attached to Berk Exhibit 1, the box that says EPO gene expressed in mammalian cells January 1984?

A. I don't know if it's referring to this specific experiment. It's certainly in the same time frame. Again, EPO was also expressed in 293 cells. But -- it may have been at a similar time frame. 02:55:05

Q. So you don't know what you are referring to in Berk Exhibit 1 demonstrative when you say demonstration or -- where you say EPO gene expressed in mammalian cells? 02:55:28

MS. FISHMAN: Objection; mischaracterizes testimony. You can answer. 02:55:43

THE WITNESS: No. I know that that time period, EPO was expressed in mammalian cells. I haven't reviewed the documents that prove it. You know, I have depended on these earlier documents that recorded that date. I remember it from that period, and so -- and I know that at about the same time, it was expressed both in COS cells and 293 cells. 02:56:01

Q. BY MS. CARSON: And when you say those earlier documents that recorded that date, footnote No. 4 refers to an interference? 02:56:16

A. It references footnote No. 4, yes.
Q. And footnote No. 4 refers to an interference decision, correct?
A. Well, again, I'm not the lawyer. And that, I would guess that from what is written here, but I'm not exactly certain of the meaning of the term. 02:56:39
Q. So you really don't know what information underlies this demonstrative?
A. Well, I do. 02:56:51
MS. FISHMAN: Objection; mischaracterizes his testimony. You can answer.
THE WITNESS: Well, I do because I was there at the time. I remember these events, and so I was happy to accept that there was evidence demonstrating that this was the date of the demonstration. 02:57:06
Q. BY MS. CARSON: So you're relying on your personal knowledge for the dates on this time line, correct? 02:57:20
MS. FISHMAN: Objection; mischaracterizes testimony.
THE WITNESS: No. I mean I'm relying on the dates that were taken from material with the indicated references. But I am relying on the people who gave me those references and those dates 02:57:40

that they are correct and that they have been substantiated; that these conclusions or this history has been substantiated.

Q. BY MS. CARSON: You're relying on the lawyers for this demonstrative, correct? 02:58:00

MS. FISHMAN: Objection; mischaracterizes testimony. You want to take him to his report, it's laid out in the report, Pat. I'm not sure what your questioning here is all about. 02:58:14

Q. BY MS. CARSON: You can answer the question, Dr. Berk.

A. I'm relying on my recollection of the events and, for the precise dates, I'm relying on the dates that were given to me in materials by a number of different people, all having to do with this case. 02:58:39

MS. FISHMAN: Do you want to take a break?

MS. CARSON: We can keep going if you like.

MS. FISHMAN: Just looks like you wanted to take a break. 02:59:10

MS. CARSON: I'm fine. We can continue.

Q. BY MS. CARSON: Dr. Berk, you've referred several times to the fact that you were involved with this project from its inception. Correct? 02:59:29

A. Yes.

Q. And do you know when Dr. Lin obtained his first patent relating to his cloning of the erythropoietin gene?

A. I would have to look at the patent to determine the date. 02:59:47

Q. If you could direct your attention to Berk Exhibit 7.

MS. FISHMAN: Are we done with Berk Exhibit 13? Pat, can we go off the record. 03:00:35

MS. CARSON: Sure.

THE VIDEOGRAPHER: We're going off the record at 3:00 P.M.

(Brief interruption.)

THE VIDEOGRAPHER: We're back on the record at 3:01 P.M. 03:01:57

Q. BY MS. CARSON: Before we went off the record, I believe I asked you to look at Berk Exhibit 7, which is the first issued of Dr. Lin's patents relating to his work cloning the EPO gene. Does that refresh your recollection as to when that patent issued? 03:02:13

A. Is the date of patent listed at the top equivalent to the date of patent issue?

Q. Yes. 03:02:30

A. Well, then yes, it refreshes my memory.

A. Just my knowledge about what was known at the time and where, where I would expect a second year post-doc to know of the literature.

Q. So in your view, you, as one of extraordinary skill in the art, would have chosen mammalian cells, but the rest of the skilled practitioners in the art knowing that they wanted to obtain an in vivo biologically active erythropoietin would not have known to choose mammalian cells; is that correct? 04:59:34 04:59:52

MS. FISHMAN: Objection; mischaracterizes testimony.

THE WITNESS: It's not that they wouldn't have known to choose mammalian cells or to try mammalian cells. But they thought that it might be possible to get biologically active material from E.coli or yeast, and so they wanted to try those as well, and then find the best source for in vivo biologically active material. 05:00:00 05:00:19

Q. BY MS. CARSON: But you knew at the time that it wouldn't be possible to get biologically active material from E.coli or yeast. Is that correct?

MS. FISHMAN: Objection; misstates testimony. Lacks foundation. 05:00:31

THE WITNESS: All right. We knew that there was this report from Goldwasser that deglycosylation of the human urinary EPO eliminated its biological activity. But that was a single 05:00:51
report and there was a possibility that the reason for the loss of the in vivo biological activity was due to some other consequence besides the removal of the sugar groups that wasn't known, and so because of that, there was the hope that it might be 05:01:10
possible to express in vivo biologically active material from E.coli, so that's why they went ahead with trying to do that. They were never successful.

There was also the possibility that the protein produced in yeast might be able to have the 05:01:31
carbohydrates removed and have biological activity because the, the result from Goldwasser and Margaret Dordal was again a single result, so it was possible that that conclusion was incorrect.

Q. BY MS. CARSON: But isn't it true that the 05:01:57
first cell type that Dr. Lin expressed human erythropoietin in was mammalian cell?

A. No. It was expressed in E.coli, I believe, first.

Q. It was expressed in E.coli first? 05:02:13

A. Yes.

Q. And it's your view that he expressed it in E.coli because he had the hope that it would be biologically active expressed in E.coli?

A. Yes. 05:02:32

Q. And what is that based on?

A. What is my conclusion based on?

Q. Yes.

A. I mean it was his goal to get biologically active erythropoietin. And he was therefore trying 05:02:47 to express it and, as the head of the team there were attempts to express it in these three very different kinds of host cells in order to see which one of them would give good in vivo biologically active material. 05:03:04

So the available results argued that E.coli would not be able to produce biologically active material. But it was possible that the conclusion was wrong and, obviously, if it had been observed, then it would have disproven the other earlier 05:03:22 conclusion.

MS. CARSON: Why don't we take a five-minute break.

THE VIDEOGRAPHER: We're going off the record at 5:04 P.M. 05:13:47

(Recess taken.)

THE VIDEOGRAPHER: We're back on the record at 5:14 P.M.

Q. BY MS. CARSON: Dr. Berk, if you could direct your attention to what was marked as Exhibit 13. 05:14:42

A. Here we go.

Q. And looking at the Bates page, I'm in the section that's entitled EPO time table on the first page. 05:15:38

A. Yes.

Q. And if you could direct your attention to the page ending in 091, it's the big number at the bottom of the page right-hand side.

A. Yes. 05:15:50

Q. It indicates on this time table, January 10 through 17, 1984, "human EPO expressed in COS cells using human genomic DNA." Do you see that?

A. What was the date? January 10th, yes.

Q. Yeah. And I think we discussed that entry before. Then if you could turn to the next page, there is an entry at March 1st, 1984 where it says "in vivo biological assay of recombinant human EPO." Do you see that? 05:16:12

A. Yes. 05:16:40

Q. And then the next entry, and that's dated

March 1st, 1984, correct?

A. Yes.

Q. And I believe that that date is also on your demonstrative time line that was attached to your Responsive Expert Report that's been marked as Berk Exhibit 1? 05:17:00

A. Yes. We just marked it, March.

Q. Right. So based on these documents produced by Amgen, is it your understanding that the first human EPO that was expressed was actually expressed in COS cells and was determined to be in vivo biologically active by March 1st, 1984? 05:17:21

A. According to the dates here. I knew it was in early March. I didn't realize it was March 1st. 05:17:48

Q. And then if you look down further on the page, it ends in 092, you'll see a date, May 16, 1984.

A. Yes.

Q. And there it says "human EPO expressed in E.coli." Do you see that? 05:18:00

A. Yes.

Q. So I believe you testified that Dr. Lin first expressed in E.coli and then changed to COS cells. Do you wish to change your testimony? 05:19:16

A. Well, according to this, it does appear

that at least the first time it's listed in this table is May 16.

Q. And I'm going to ask the reporter to mark as Berk Exhibit 21 a copy of Dr. Lin's testimony taken in this litigation dated March 28, 2007. 05:19:41

(Deposition Exhibit No. 21 was marked for identification.)

Q. BY MS. CARSON: If you could direct your attention to page -- these are done four per page in this document, so if you could go to Page 50 or the page that has Page 50 on it. And if you could just read through pages 50, 51, 52 and 53 that are all on that one page to yourself. 05:20:30

A. All right. All right. 05:23:51

Q. Having now read Dr. Lin's testimony, does that indicate to you that in fact the first cell type that Dr. Lin cloned the EPO gene in was a COS cell?

A. Well, no. The first cell type in which he expressed the EPO polypeptide was a COS cell. I mean in fact, gene was originally cloned in E.coli, but they didn't make any attempt to test for expression in E.coli apparently. 05:24:08

Q. So why would the gene have been cloned in E.coli? 05:24:24

A. Well, you just use E.coli cells for doing cloning.

Q. That's just to isolate the gene itself?

A. Yes. 05:24:33

Q. And why do you -- at the time would one use E.coli cells just to isolate the gene?

A. All the methods for doing gene isolation depended on using E.coli cells.

Q. But the first cell type that Dr. Lin tried 05:24:50 to express the gene encoding human erythropoietin was a COS cell, correct?

A. Yes. I stand corrected on that from reading this testimony. I thought because there was so much expertise in expressing in E.coli, and it 05:25:08 was a straightforward thing to do that they would have done that, but apparently they did the COS cell expression first.

Q. It was in the COS cells that they demonstrated that it was in vivo biologically 05:25:21 active, correct?

A. Correct.

Q. And then according to the time line, several months after that, it was, was when Dr. Lin attempted to express the human erythropoietin in 05:25:39 E.coli, correct?

A. According to the time line. Where did the time line go. Here, yes.

Q. That was Exhibit 13.

A. It was not until -- we just found it before. 05:26:00

Q. I think it's on the page that ends in 092. It's the fourth entry up from the bottom.

A. Right. So that was May 16.

Q. Okay. So it was actually a couple of months after he knew that he had expressed biologically active erythropoietin in COS cells that he tried to express human erythropoietin in E.coli cells, correct? 05:26:19

A. The first expression in COS cells was just detected by radioimmunoassay which wasn't an assay for in vivo biological activity. 05:26:38

Q. Right.

A. That wasn't done until later. So I'm trying to check the dates. Right. So it says that March 1st was the in vivo biological assay. 05:27:01

Q. And then a couple of months after that, Dr. Lin went on to express the human EPO in E.coli, correct?

A. Yes. 05:27:13

Q. Do you have any understanding why he would

have then gone to attempting to express the human erythropoietin in E.coli when he knew he had a biologically active product from COS cells?

A. At that time in particular, if it had been possible to express biologically active protein in E.coli, it would have been preferable to expressing it in mammalian cells. 05:27:30

Q. And why is that?

A. There was much more experience with protein expression in E.coli. The science was much more highly developed. One could make an even higher percentage of the total protein, the protein of interest in E.coli, and then also there was concern at that time about the possible contamination of mammalian cell cultures with human pathogens, and so there was that -- that caused the FDA to scrutinize products made in human cells or mammalian -- cultured mammalian cells much more extensively than products made in E.coli. In fact, they were still working out the rules for products made in mammalian cells. 05:27:44 05:28:05 05:28:29

Q. It wasn't the uncertainty as to whether or not he could obtain a biologically active protein in mammalian cells that led him to also use E.coli, but it was just the industrial advantages that were 05:28:47

known to be associated with E.coli. Isn't that correct?

A. Yes. The main reason was to determine if it could have been produced in biologically active form in E.coli, right, for those practical reasons that we discussed. That would have been the reason for making it in E.coli. E.coli would have been much easier to scale up very rapidly, to produce a product sooner if it could have been made in E.coli. 05:29:06 05:29:28

Q. Okay. I'm going to ask the reporter to mark as Exhibit 22, Berk Exhibit 22, a letter to me from Deborah Fishman received on June 6, 2007.

(Deposition Exhibit No. 22 was marked for identification.) 05:30:26

Q. BY MS. CARSON: Dr. Berk, I received this letter with corrections to your May 11 expert report. And did you ask to have these corrections made?

A. Yes. 05:30:46

Q. If you could turn to paragraph 58.

A. In the -- in No. 8 or No. 1.

Q. Yeah. In Berk No. 8.

A. Paragraph 51?

Q. 58. 05:31:27

A. Yes.