EXHIBIT 15

PART 2 OF 2

HIS HONOUR: It was a gloss, as lawyers would say?

DR BENNETT: A total gloss. It made no difference whatsoever to what you would need to being able to do anything with what is described in the patent. Our evidence basically is that molecular biologists wouldn't care and wouldn't be able to do anything within it, it wouldn't affect any molecular biology, and an experienced protein person, or an experienced sugar person, our evidence is, would take one look at it and say, "No, 15.09 mammalian protein from mammalian cell, not on, can't be right," because it has never been heard of before or since.

MR CAINE: My learned friend, in response to an identical question from your Honour at page 241 of the transcript, also said to your Honour that there was an issue of inherency. If my learned friend would deal with that to assist me, your Honour.

DR BENNETT: Yes. We also say that this carbohydrate composition data - these. I had a professor who was obsessive about these data.

HIS HONOUR: This data?

DR BENNETT: No, it is datum and data. It was the only thing I brought out, I suppose, of my whole science course, one the few things, was to say "these data". Although I hear in the news they keep talking about referendums.

HIS HONOUR: I decline to comment.

DR BENNETT: I never did Latin either. There is an issue in the law, we say, that there have been cases decided that say if what you start with inevitably gives you something that is correct and you mischaracterise it, either because you make a mistake in analysis or because the ability to do that sort of analysis wasn't available at the time you put on your patent but that what you would get inevitably would lead to a correct result, you are entitled, notionally or even in reality, to amend. If you give evidence to a court that says, "These data are wrong and here's an explanation, to the extent that I can give one, of how I got these wrong data," or you can establish that it is likely that the data are incorrect and that that is not what you should have got, it doesn't go against what you can claim because, in fairness, you got the right thing, you have just mischaracterised it, and that is the inherency concept. I don't have the case in front of me, but that is the inherency concept.

HIS HONOUR: Mischaracterised it in the claim?

DR BENNETT: You mischaracterise it in the claim and in the body of the specification. One example, your Honour, it's a simple example that arose in a case where a chemical formula was given and as they went through - you can get chemical formulas, what are called N or iso, it just whether you say the structure is this way or that way, it is the same basic thing. The patentee made

the mistake of saying, "I believe what I have got is isopropyl". In fact, they were wrong, and it was N-propyl. Another party came along and said, "Ha, ha, we have now have the correct characterisation, so we can have this product and you can't have it, because you've claimed a different product".

What was established in the court was that if you started with what we started with in the patent and followed through, you inevitably got the correct result. So the court allowed that patentee to fix it up and then to prior claim the subsequent product that disclosed the correct formula.

HIS HONOUR: There is a Latin maxim analogous to this falso emonstratio non nocet.

DR BENNETT: I get the first bit. I remember the maxim, but I never remember exactly what it meant. I will check it out, though.

Of course, our case is different because our case is an easier case than the one I just cited to your Honour because here the claim themselves, or claim 39, does not itself recite a mischaracterisation nor does it need to do so, because there is other evidence. In the case I referred to, they actually claimed the wrong thing specifically by referring back to the wrong thing, from my recollection. Here, we don't mischaracterise anything in the claim and there are two pieces of information in the specification that reflect it and even if one is wrong, one still has the other one that we rely upon, which are the molecular weight data.

There are other legal arguments of course that will be saying, for example, that this can't be relevant to either the sufficiency or fair basis aspects that my friend is relying upon with respect to this patent generally, but I don't need to expand upon that now.

HIS HONOUR: I was more interested to get it in a factual matrix, yes.

MR CAINE: Your Honour, can I do two things: the case that my learned friend is referring to at least, I think, is one that your Honour has recited in your Honour's interlocutory judgment, Merck v. Sankyo, a decision of Lockhart J. The reason I rise is that I apprehend that my friend is seeking in some way to amend claim 39. The statement of proposed amendments doesn't appear to advance that and I'm not sure - - -

HIS HONOUR: I didn't understand that to be the case.

DR BENNETT: I should just say, your Honour, we don't propose to amend. There are two cases, if we are going to mention them - I was not going to deal with them at this stage - Merck v. Sankyo is one and the other case is a decision of Gibbs J in the case of Farbwerke which is on our list of authorities. If your Honour wishes to see them, we ultimately have folders of cases we will be handing to your Honour.

HIS HONOUR: We will deal with that later. Mr Caine, we have eaten into your lunchtime preparation time a bit so we will resume at 20 past.

ADJOURNED **[12.50 pm]**

AM 67 024594
CONFIDENTIAL

RESUMED **[2.20 pm]**

DR BENNETT: I have one question for Dr Haselbeck in cross-examination, your Honour.

Dr Haselbeck, if you wished to detect differences in the carbohydrates between two glycoproteins as at 1983, using methods other than SDS page, you could use isoelectric focusing?---You could.

And you could selective binding to lectin columns?---You could.

DR BENNETT: No further questions.

<RE-EXAMINATION BY MR CAINE

Dr Haselbeck, my learned friend asked you some questions concerning the carbohydrate data that is reported at page 64 and page 65 of the specification. In response to one of her questions, you said that one of the things that had influenced your construction was the context of the specification and, in particular, that a precise claim had been made based on the carbohydrate data there reported. Could you indicate for His Honour what you meant when you referred to a claim based on that data?---I was referring to claim 39 in that regard.

My learned friend then asked you some questions again about the carbohydrate data that was reported on page 65 of the specification, and you said that you had seen in Dr Lin's notebooks two samples that had been analysed and that the data from the second sample was the data that was put into the patent. Do you recall that line of questioning?---Yes.

My learned friend then asked you some questions about one of the pages from Dr Lin's notebook, and that was page AU0355; do you recall that?---Yes.

Could I hand to Dr Haselbeck a copy of page AU0355. Do you see that document, Dr Haselbeck, is headed "Analytical results of carbohydrates"?---Yes.

There are there set out three glycoproteins entitled A, B and C?---Yes.

Would you indicate to His Honour in relation to each of those glycoproteins whether it is a recombinant product or a urinary product, starting with glycoprotein A?---There is a note, a handwritten note, on the left lower corner, it says A is human urinary EPO, that is glycoprotein A. Then B, CHO EPO purified, so that is a recombinant product from CHO cells, I would assume. Then C CHO EPO purified and a few other indications. So that means glycoprotein A was referring to the urinary erythropoietin one being isolated from human urine; glycoprotein B and C to two samples of CHO expressed and obviously purified erythropoietin samples, being analysed by Dr Yu.

Based on what you have seen from Dr Lin's notebooks and the discovered documents that accompanied them, what do you say as to the analysis of the samples which are labelled glycoprotein B and glycoprotein C?

DR BENNETT: I object. I did cross-examine on this document; I have no problem with that. There was a reference to a piece of information in answer in cross-examination generally referred to by the witness. I did not cross-examine on all of Dr Lin's notebooks and all of the material that may have been produced on discovery, and I object to my friend now raising some general matter in re-examination, "Based upon everything else that you have read, what do you say about this?" It is not proper re-examination, in my respectful submission.

HIS HONOUR: How is it put?

MR CAINE: I can be more specific, your Honour. This witness was asked questions about the carbohydrate data that is reproduced on page 65 and he said he had examined Dr Lin's notebooks and based, on the document I have just taken him to, he says that there were two samples analysed and it was the second sample that was reported in the specification, in particular with the hexose value of 15.09, which your Honour will recall on page 65. He was challenged throughout his cross-examination about the unusual or strange nature of that figure. He said in response that it wasn't just that figure, he had seen an earlier sample analysed, and I think his evidence was that it had similar numbers.

DR BENNETT: It was this one. I asked Dr Haselbeck what he referred to and he referred specifically to two pages, and this was one of them. He didn't do a general canvass through the evidence. I don't know what my friend is going to.

HIS HONOUR: It is established that this is the page he was referring to, and is it common ground that it bears out what he said?

MR CAINE: I am not sure about that. I wanted to establish that sample B had been earlier analysed and that, following that analysis, C was analysed, and it was only then that 15.09 was reported as the hexose ratio.

DR BENNETT: Your Honour, that clearly goes beyond cross-examination. We were talking about this page, this is the page that he referred to, and in re-examination it is inappropriate to go beyond that. The material I cross-examined on is here, quite clearly, and the witness didn't take it beyond this. We talked about this page and he raised the page and then I asked him questions about that page, and that's what he relied upon.

MR CAINE: That is not a proper characterisation, in my respectful submission, of this cross-examination. He said that there were a range of pages and he said 340-348, some eight pages. It now transpires that in fact he was

referring to the wrong page, but he was referring to more than one.

HIS HONOUR: This is the page that he had in mind?

MR CAINE: It is one of the pages, your Honour. There are two other pages which make clear the sequences of sampling. That is all I seek to introduce, those other two pages. It is my friend's document.

HIS HONOUR: What do you want to ask him about this page?

MR CAINE: Simply that glycoprotein B, on his understanding of the documents, was analysed beforehand and the hexose value of 16.98 was arrived, and it was only after it was reanalysed and 15.09 was the figure that was then ascertained that that second analysis was the subject of what was reduced into the patent specification itself.

HIS HONOUR: You can ask him, in what I might naively suggest now, is a non-leading manner.

MR CAINE: Sorry, your Honour.

HIS HONOUR: How this page led to the impression that he gained, that he spoke about, that he gained from Dr Lin's notebook.

MR CAINE: It isn't just this page, there is other correspondence that shows that two samples were conveyed. The simplest way is to introduce the other two pages that make that clear. I don't think my friend can resile from that, your Honour.

HIS HONOUR: All right.

MR CAINE: Dr Haselbeck, can I show you pages 350 and 352 of the discovered documents. If I go first to document 350, Dr Haselbeck, is that a document which bears in its top right-hand corner the date 31 October 1984? ---Yes.

Is there a reference there to two samples, A and B?---Yes.

Is that the document that led you to conclude that samples A and B were sent for analysis?---Yes.

Can I take you now to document 352, which bears in its top right-hand corner the date 20 November 11984?---Correct.

Is that the document that led you to conclude that sample C was sent for analysis on that date?---Correct.

Can I take you back to document 355 and to the reference to glycoprotein B. Is

the reference there to glycoprotein B and the value of 16.98 which is shown as the molar ratio for hexose, is that a figure that appears in the patent specification on page 65, to your knowledge?---No, it doesn't.

If you go to glycoprotein C, the molar ratio there shown for hexose as 15.09, is that a figure, to your knowledge, which is reported on page 65 of the specification?---This is the exact figures which are reported in the specification.

MR CAINE: No further questions in re-examination

HIS HONOUR: Whose notebook is it?

MR CAINE: Dr Lin's notebook.

DR BENNETT: Are you tendering all these pages?

MR CAINE: Yes.

EXHIBIT #G - COPIES FROM DR LIN'S NOTEBOOK PAGES 350, 352 AND 355

HIS HONOUR: Thank you, Dr Haselbeck, you are excused.

<THE WITNESS WITHDREW [2.35 pm]

MR CAINE: The next witness that I seek to call is Henrik Steen Olsen, who has sworn two affidavits. They appear in court book volume 6. Can I check that your Honour has both affidavits incorporated in the court book. The first one should appear at page 1331 and the second one, I hope, is in your Honour's court book at 1334A.

HIS HONOUR: Yes, I have those.

MR CAINE: I might read into the transcript, for the benefit of my learned friend, whose court book doesn't have the additional pages, that Dr Olsen's second affidavit spans the pages between 1334A and 1334F.

AM 67 024598
CONFIDENTIAL

<HENRIK STEEN OLSEN, affirmed **[2.37 pm]**

MR CAINE: Dr Olsen, that is not an amplifying device, it is a recording device, so could you as best you can, keep your voice up and direct your answers across to His Honour on the bench. When you come to technical terms in your explanation, if you could show mercy on the court reporters, who, at times, might need you to travel a little slowly so they can pick them up accurately?---Yes.

Do you have a copy in the witness box of your first affidavit? Do you have the court book there, a grey bound book that has volume 6 on the front?---Yes.

Can I take you to page 1331 of the court book?---Yes.

Will you tell His Honour your full name and address, please?---My full name is Henrik Steen Olsen and my address is 182 Kendrick Place, No. 24, and that is in Gaithersburg, Maryland, USA.

Is that the address that appears on the first and second lines of the affidavit that I have just taken you to?---Yes, it is.

Did you swear that affidavit in these proceedings on 27 October 1997?---Yes, I did.

Did you also swear a second affidavit which appears on court book page 1334A?---Yes.

Did you swear that on 22 April 1988?---Yes.

1998, sorry?---Yes, I did.

MR CAINE: Your Honour, my learned friend has a formal objection, which it may be appropriate to canvass now before the evidence commences.

DR BENNETT: Your Honour, we object to the whole of this affidavit. The affidavit cannot be relevant to any matter before this court, as it relates only to work that was done and could be done well after either of the dates in question, which are 1983 and 1985. Further, this evidence does not purport, on its face, to be any attempt to repeat or use the information in the Kirin-Amgen application. Accordingly, the entirety of this evidence has absolutely no relevance. Nor could it be said in any shape or form that Dr Olsen could be a relevant witness for the purpose of these proceedings.

MR CAINE: Your Honour, the evidence is introduced for this purpose: your Honour will recall I opened, amongst other things, that an issue in the case was the ease or otherwise with which a person could identify relevant messenger RNA, that is EPO mRNA, so as to construct a cDNA library. One of the issues therefore was whether one could find a suitable tissue source to permit that to

be done; another was whether COS or CHO expression systems could provide that tissue source.

Putting it briefly, your Honour, the case by Kirin-Amgen is that it is a simple matter, once you are seized of the data in Table VI, to build highly specific probes and probe relevant libraries. What Dr Olsen's evidence is directed towards is saying that if you use a different screening technique, which is more sophisticated than the use of oligonucleotide probes that were available with the information provided in the specification, you still would not, in a large number of cases, find relevant message or cDNA. We say that that bears directly on the ease or otherwise with which it could be done. The fact that it has been done after the event, with more sophisticated technology than was previously available, simply heightens the strength of our proposition, far from demeaning it.

HIS HONOUR: I will receive it, subject to objection. Even if what you say is correct, it doesn't necessarily follow that a more advanced technology is better for this particular purpose. I don't know.

MR CAINE: I think ultimately it is a matter for weight and submission, or perhaps admissibility in the course of submissions. I have no further evidence-in-chief.

<CROSS-EXAMINATION BY DR BENNETT

Dr Olsen, just trying to assess the relevance of your evidence: are you saying that you are here today to say that in 1983 or in 1985, it was not possible to obtain a cDNA in any source using the information in the Lin patent?---I think I can say that, based on what we know from our sequencing, it would be difficult to do that.

Are you here to say that as at 1983 or as at 1985, it was not possible to obtain a cDNA in any source using the information in Dr Lin's patent application or the Kirin-Amgen patent application?---Can you repeat that question.

Are you saying that you are here today to say that in 1983 or in 1985, it was not possible to obtain a cDNA from any source using the information in the Kirin-Amgen patent application?---If you had a reliable source to get - - -

HIS HONOUR: Sorry, I can't hear you?---If you had a reliable source of your messenger RNA, you could certainly do that.

DR BENNETT: Dr Olsen, what were you doing between 1983 and 1985?---We were - - -

No, you personally?---I was involved in constructing cDNA libraries and I was involved in analysing the EST data, the EST sequence data we obtained from the cDNA libraries.

Were you doing EST sequence data work in 1983?---Okay, I thought you said 1993.

Let's start again. What were you personally doing in 1983?---I was in school studying molecular biology.

When you say you were in school, were you in university?---Yes.

What year of university were you in in 1983?---I was in my fifth year.

And in 1985?---I was still at the University of Aarhus in Denmark, studying molecular biology.

You received your PhD in 1990?---Yes.

How many years did you spend doing your work as a graduate student?---Studying for my PhD?

Yes?---I spent 3 years, as far as I remember. It may have been - - -

So you started doing your PhD work in about 1985-1986?---Yes.

Are you here as an independent scientist or as a representative of Human Genome Sciences?

MR CAINE: What is the difference? Plainly they are not a party in the proceedings. He must be independent, your Honour.

DR BENNETT: Your Honour, my friend is seeking to put on other evidence through this witness, work that was done at this company, and we are entitled to know whether he is here purely in his own capacity or representing that company.

HIS HONOUR: You had better clarify what you mean by "representing", but I think the question is admissible, subject to that.

DR BENNETT: Are you here to talk about the work generally that is done at Human Genome Sciences?---Yes, I am here to talk about it.

When was that company started?---It was started in 1992.

In your affidavits, you describe using, in broad terms, the techniques of EST or expressed sequence tags data base searching for EPO sequences?---Yes.

And you also describe PCR, or polymerase chain reaction, techniques to search some cDNA libraries?---Yes.

For erythropoietin sequences?---Yes.

Were either of these techniques available in the period of 1983 through to the end of 1985?---The PCR reaction technique became available in the 1980s, as far as I remember. Precisely when, I do not remember. The EST sequencing was developed probably very early in maybe 1990, or a little bit before that.

Is it fair to say that PCR techniques were not generally available until the late 1980s?---It may be so. I cannot remember the exact time it became available.

Is it fair to say that PCR is a technique applicable to the sort of thing you described here, where, after you obtain a hit or a hybridisation, after you obtain that, you can amplify it using PCR?---Yes, you can amplify a target sequence you are interested in.

First, you have to get the target sequence and then, for the ease of identification, you can amplify it?---Yes.

If you don't get a target sequence, there is nothing to amplify?---Yes. You have to know some sequence information about your target sequence.

You have to get a hit, you have to identify, by using whatever you are using to go in to get the sequence out of your library, you have to find it first before you can amplify it?---By PCR, yes.

Are you aware that in the period of 1983 to 1985, workers in the field of molecular biology, again in broad terms, identified specific cDNA clones by probing cDNA libraries?---Yes.

And those libraries were made from messenger RNA isolated from cell lines, tissues or transfected host cells?---Yes, I am aware of that technique.

What were used there were probes specific for the gene of interest?---Yes.

Have you yourself read the Kirin-Amgen application?---Yes, I have read that application.

Did you try to follow the methodology taught in the patent?---No, I did not.

Did you attempt to identify cDNA clones for EPO in any of the 250 cDNA libraries you claimed to have access to by probing these libraries with a radiolabelled probe specific for erythropoietin?---No, we did not try to isolate it by probing. What we did was to analyse our library by sequencing a huge number of cDNAs from these libraries.

Did you do a northern analysis of messenger RNA isolated from various tissues and cell lines using EPO specific probes to identify cell or tissue types that express EPO?---No, we did not.

Did you prepare a cDNA library from a genetically transformed host cell, such as COS or CHO cells, that express the EPO from an EPO genomic gene clone?---No, we used libraries that are made from natural sources, which is human tissue samples.

Does your affidavit describe the work that was set out in the letter that you annex to your affidavit from Dr Rosen to Dr Schumacher?---Can you repeat that question, please.

Does the work that you describe in your affidavits describe the same work that was set out in the letter that you annex from Dr Rosen to Dr Schumacher? ---Yes, I believe so.

Let me go to the libraries for the moment, if I may. Mr Rosen says in his letter, which is at page 1336 of the court book, that the partial cDNA sequences were obtained from kidney cDNA libraries. Do you see that?---Yes.

Were they adult kidney cDNA libraries?---It was adult kidney libraries and it was foetal kidney libraries.

So it was a mixture of adult and foetal kidney, in that kidney library?---No, it was different libraries, as he says, "cDNA libraries". I think what he is trying to say in that statement is that we sequenced a library originating from adult kidney and foetal kidney.

Right. Were there different libraries that came from normal adult tissue?---Yes, it was.

And normal foetal kidney tissue?---Yes, it was.

It refers there also to malignant tissue; was that adult or foetal?---That was probably both.

Do you know? You say "probably both". Are you guessing, or do you know?---I am basing that - I would say it was both. Can I elaborate a little bit on this?

Are you saying that there was one library made from malignant adult tissue and other libraries made from malignant foetal tissue?---We have a huge number of tissues coming from malignant - a huge number of cDNA libraries coming from malignant tissues - and I cannot remember in detail exactly how many are from adult and how many are from foetal tissues.

But all of the libraries we are referring to here, as set out by Dr Rosen and, as you say in your affidavit, are kidney cDNA libraries?---Can you repeat that question, please.

The libraries that are referred to by Dr Rosen in his letter and as you refer to

when you refer to this same work, were kidney cDNA libraries?---Not all the 250.

Where does Dr Rosen say here that there were libraries other than kidney cDNA libraries?---What he says is that we have sequenced cDNAs from over 250 cDNA libraries, and that includes a library from adult kidney, foetal kidney, and adult liver and foetal liver.

Sorry, I must have missed something. Where does he say that it has adult and foetal liver in this letter?

MR CAINE: That is not a fair question. I can put this in the absence of the witness - it is difficult to put it while the witness is here.

DR BENNETT: I am happy to go through his affidavit as well. I am asking him now what Dr Rosen says here.

MR CAINE: It the context of the letter itself. I am not seeking to resort to the affidavit. The sentence itself doesn't suggest that it is confined to kidney.

HIS HONOUR: Why can't he be asked about the letter?

MR CAINE: My friend is putting propositions that, in my respectful submission, are not predicated on what the letter says.

DR BENNETT: The witness has repeated this in his affidavit, he has referred to his work, he is here to talk about it, he has annexed the letter.

HIS HONOUR: I think he can be asked about the letter. He has adopted the letter.

DR BENNETT: Is there anywhere in this letter, Dr Olsen - it says here that over 3,000 sequences were obtained from kidney cDNAs libraries. Do you see that?---Yes.

"In total we have constructed over 250 cDNA libraries that represent normal and malignant tissue, foetal and adult tissue and specialised cDNA libraries"?---Yes.

Did you agree with me there is nothing there that says that those libraries came from any tissue other than kidney tissue?—I have difficulty answering that question. I am not quite sure that I understand what Dr Rosen is trying to say here.

So far as the malignant tissue was concerned, was that malignant tissue specially made to produce erythropoietin?---No, it wasn't. It was tissue obtained from different government organisations that provide tissue for research institutions and companies that want to analyse these samples. As it is human tissues, you

cannot get to order so to speak.

So it is just some form of malignant tissue?---Yes.

Let's see if we can turn to what you or HGS do. Perhaps for the court's assistance, and certainly ours, we would like to understand what express sequence tags are and how one uses EST data bases. I am going to ask you some questions directed to that. Let's start with your cDNA libraries used for obtaining your EST data base. You start by isolating messenger RNA from a cell or tissue source?---Yes.

You don't use, as a source, transfected host cells?---No, we don't.

Do you use oligo (dT) primers or random primers?---We use mostly oligo (dT) primers.

Do you sometimes use random primers?---It happens, but not very often.

If you use oligo (dT) primers, you prime cDNA synthesis using an oligo (dT) primer which initiates the synthesis at the very 3 prime end of the messenger mRNA at the poly(A) tail?---Yes.

The cDNA is then made double-stranded?---Yes.

And cloned into a vector?---Yes.

Do you size-select the double-stranded cDNA prior to cloning?---Yes, we do.

What is the average size and targetted range of sizes for your cDNA clones?---The average size - and now I am talking about these manual libraries - is, I would guess, around 1.5 to 2 KB.

Do you attempt to make a full length cDNA and obtain full length cDNA clones?---Yes, we do.

Is it fair to say, however, that in many cases the cDNA clone that you obtain starts at the 3 prime end but is not full length through the coding sequence?---Some of them will not be full length sequences, which is actually in certain cases an advantage to us.

But to the extent that you do not have full length sequences, is it fair to say that the library is biased towards the 3 prime end of the mRNA?---The libraries themselves, due to the way you generate the cDNA clones, will be biased to the 3 prime end. However, what we are doing is that we are sequencing from the 5 prime end, so what - - -

so You sequence from the 5 prime end as well as from the 3 prime end?---We sequence from the 5 prime end.

As well as from the 3 prime end?---We normally do not sequence much from the 3 prime end.

Okay. How much sequencing do you do from the 5 prime end? Do you get all of the 5 prime to 3 prime end or just some of the 5 prime end?---What we normally do is we make a single sequencing reaction from randomly selected clones, and that is how an EST sequence is defined. Based then on analysis of that sequence, we try to identify the cDNA clone; and if we think it has some kind of potential interest, we will then go ahead and sequence the rest of it.

Do you actually sequence from the 5 prime end the entire coding sequence?---In certain cases, yes.

But in certain cases, no?---Yes.

Is it fair to say that a number of your ESTs would have a sequence lengths of, say, 200 base pairs?---The average length is about, I would say, 400 to 500. So there will be a spread, of course; some will be longer, some will be shorter. Yes, you can say a percentage of them will be 200 or shorter.

So would it happen that sometimes with this randomisation, you would get two different ESTs that relate to the same gene?---Yes.

Or you might get more than two ESTs that relate to the same gene?---Yes.

I think you said that these ESTs are sequenced and put in a data base?---Yes.

If I understand correctly, for a given cDNA clone, all or part of the partial cDNA clone is sequenced and that sequence is entered into the data base; is that correct?---Can you repeat that question.

That for a given cDNA clone, all or part of the partial cDNA clone is sequenced and that sequence is entered into the data base?---Yes, that's correct.

You said in your affidavits that you searched a data base containing 60,000 partial cDNA sequences for EPO related sequences?---Yes, that was in Dr Rosen's letter.

How many different genes do you think are represented in the data base of 60,000 sequences?---That's a very difficult question to answer; it's a very broad and very difficult question to answer.

You certainly wouldn't expect that the 60,000 sequences represented 60,000 different genes, would you?---That would probably be unlikely, depending on of course what source they are generated from. If they are from a number of different sources, as it was in this case, they would probably represent a very high number of individual genes.

But you can't really estimate what sort of number of individual genes you have represented in your 60,000 sequences?---You can estimate it by analysing the sequence, and there will be sequences in it that are known human genes and from that you could make an estimation of the number of individual genes.

But without that information, you can't say how many unique genes are represented in your 60,000 sequences?---No, you would have to make that estimation.

Is it fair to say that your evidence is that the cDNA clones are randomly selected for sequencing?---That's correct, they are randomly selected for sequencing.

Doesn't that mean that if selection is random, that it is more likely that a highly-expressed gene is more likely to be selected for sequencing than a rarely-expressed gene, like erythropoietin?---The abundance or the frequency of which an EST comes up in a data base will be the same, at least in theory, to the frequency of that RNA in the tissue from which the library was generated, and that is very important information.

Just help me with this. Does that mean that if you have more message for EPO there and it is random - - -?---You would be more likely to pick it up when you sequence ESTs from that particular library.

And if there is less EPO there, you would be less likely to pick it up?---Yes.

You also stated that you had prepared over 250 cDNA libraries?---Yes.

Just with simple mathematics, does that mean that if you started off with 60,000 sequences and you prepared about 250 cDNA libraries, that that would mean that you have an average of only 240 sequences from each library represented in your data base of 60,000 sequences?---Yes. These numbers come from the very beginning of the company, and we have now generated a very large number of cDNA libraries and a very large number of EST sequences. But these numbers come from the very beginning of the company, and if you do that calculation, yes, you're right.

Is it fair to say that you can't say today how many unique sequences are represented in the libraries?---"How many unique sequences"?

Unique sequences are represented in the libraries?---We can make an estimate.

But you can't say for sure; you don't know precisely?---We cannot say for sure. I can add that nobody knows how many genes actually are in human cells, so every number will be an estimate.

Well, access to the NIH home page suggests that there is an estimated 100,000

different expressed genes in the human genome?---Yes, and - - -

Do you agree with that sort of estimate?---Yes, and I can add that we estimate in our company that we have maybe 95 per cent of these human expressed genes represented in our data base.

That is not the data base that you used for the work described in your affidavits, is it?---No. At that point, the data base was under development.

So we are still talking about the figures that are in your data base, which is the 60,000 sequences that you refer to, which we have agreed do not represent 60,000 unique sequences and unique genes; is that fair enough?---Yes.

Okay. Bearing in mind that your library has fewer than 60,000 different genes represented and contains sequences of only some of the genes, or a fraction of the genes, expressed in a human body, are you really surprised that you didn't find EPO?---Based on the literature, it seems to be a gene where the expression is highly controlled to be expressed in certain tissues under very certain circumstances. If you asked me if I was surprised that we didn't see it, I would say probably not.

You wouldn't have expected to find a lot of EPO message in your malignant cells?---You don't really know where the ESTs eventually will show up.

You wouldn't have expected to find lots of message for EPO in your malignant cells, would you?---I can mention that of the two ESTs in the public data base that we have analysed, one of them comes from a brain library, the other one comes from, as far as I remember, a normalised foetal liver library, and that is exactly where you would expect it to show up. Contrary to that, you can actually find them in a brain library. So it is very difficult, from what is known about expression of certain genes, to extrapolate that to an EST data base like ours, where you have sequence information that comes from basically the whole body. When you are doing an expression analysis based on, for example, a northern, you are normally restricted to analysing a rather small number of samples, it may be 20, it may be 40; whereas when you build a data base like ours, you can analyse hundreds of libraries.

Some of the libraries that you were analysing were foetal kidney libraries?---Yes.

Would you have expected to find a lot of message in foetal kidney cells?---Based on the literature, that would be a possible source.

So your understanding is that foetal kidney is a recognised source of the production of erythropoietin?---I think it is expressed in foetal liver.

No, I asked you about foetal kidney?---Yes. I don't know.

So far as the foetal liver libraries were concerned, from what stage of foetal development were those libraries made?---They were made from the tissue that was available for us from these government agencies, and I cannot exactly remember what part of the development they came from.

But we still have a situation that we are looking at approximately 240 clones per library; is that fair enough?---Yes.

You further said in paragraph 4 of your first affidavit that in the 60,000 EST data base, there were 3,000 sequences derived from kidney libraries?---Yes.

Therefore 57,000 of these sequences or 95 per cent of the total were from cell or tissue types that wouldn't necessarily be expected to produce erythropoietin? ---As I mentioned before, it's very hard to actually predict where these genes will be expressed and where you will actually end up finding them, and that's why one example in the public date base of EST sequences that seems to encode EPO comes from a brain library and not the libraries where you, based on the literature, would expect them to be found. That is why I think it is important that you try to sequence a very broad range of libraries.

But it is fair to say that your libraries were not focused in terms of choosing libraries that were specifically geared to be likely to be expressing erythropoietin?---Our libraries were focused to get as comprehensive as possible a picture of human gene expression. So it is correct to say that it would not be specifically geared to identifying the EPO sequence.

Of the 3,000 sequences from the kidney, I don't think you said reading those 3,000 sequences to different kidney libraries. How many of those came from adult kidney?---I cannot precisely remember what part of them came from an adult kidney and what part of it came from the foetal kidney libraries.

Were there any kidney tumour libraries there?---I cannot say that for sure, but I think there was.

You can't say also how many of the 3,000 sequences came from that sort of source? If there was a tumour library there, how many of the sequences came from a kidney tumour library?---No, I cannot remember the exact number.

Is it fair to say, therefore, that only some part of the 3,000 sequences would have been expected to come from a cell type from which erythropoietin expression could be expected?

MR CAINE: Expected when, your Honour, 1983 or 1992?

DR BENNETT: We can't ask about 1983. This work wasn't done in 1983. The work he's doing.

Therefore it is fair to say, isn't it, that only some part of the 3,000 sequences

came from a cell type from which you would have expected erythropoietin expression to have taken place?---If you mean expected and define that as kidney and liver and foetal kidney and foetal liver, that is correct. What I tried to say before, when I mentioned the two examples of ESTs that actually positively encodes EPO, one was found in library and that is a source that you wouldn't expect, but still it shows up, and that demonstrates that it is very difficult, from the literature, to completely predict where a gene is expressed and therefore where the EST will show up. So it is a question that is difficult to answer completely.

But it is certainly fair to say that if you were looking at 3,000 sequences from all these different tissue sources and different cell types within those tissue sources, that only some part of those 3,000 would be expected to come from a cell type from which you would have expected to actually have erythropoietin expression?---Yes, you would expect the EPO gene to be expressed in very particular tissues at a certain time in development. So it is correct that you would probably not expect EPO to be found in all the libraries, that is correct.

What is your estimate of how many different unique messenger RNAs are represented in those 3,000 sequences?---It's very difficult to answer, but I would say maybe 50 per cent, in that range, maybe 75.

That is a rough estimate that you are making?---Yes.

Let me show you a page from the book Molecular Cloning, the second edition, by Sambrook, Fritsch and Maniatis. Are you familiar with that book? ---Somewhat.

This is from the 1989 edition. You have the cover page and a couple of pages inside. The authors say under the heading "Methods of Enrichment" that a typical mammalian cell contains between 10,000 and 30,000 different mRNA sequences. Would you disagree with that?---Can you repeat that.

If you read it down, it says "Methods of Enrichment" on the first of those pages: a typical mammalian cell contains between 10,000 and 30,000 different mRNA sequences. Would you disagree with that?---That is probably correct.

Being generous and assuming even that all 3,000 sequences that you were looking at were unique and came from different messenger RNAs, is it fair to say that the 3,000 sequences you searched represents only 10 per cent to 30 per cent of the different messenger RNAs expressed in a kidney or liver cell?---That is probably correct.

And for your foetal liver libraries, I think you agreed with me that you are not aware that any of them were particularly made from liver tissue from mid-term or later foetuses?---No, I am not aware that they were made specifically from that tissue.

And are you still surprised that you did not find the erythropoietin gene?---I don't know if I can answer that question.

If you turn over the Maniatis page, you will see that he says about 8 or 9 lines down, "To achieve a 99 per cent probability of obtaining a cDNA clone of an mRNA present," and in that case human fibreglass, "at a frequency of approximately 14 molecules per cell, you would have to screen 170,000 clones". Do you see that?---Yes.

You don't disagree with that, do you?---No.

The authors go on to point out that many messenger RNAs of interest are present at even lower levels. Do you see that?---Yes.

"In such cases, the frequency at which the sequences of interest are represented in the initial preparation of messenger RNA may be reduced still further and it then becomes necessary to construct and screen libraries that contain several million independent cDNA clones." Do you disagree with that?---No.

The work that was done that is referred to in your affidavit, this was work done back in 1993, was it?---Yes.

It is right, isn't it, that your libraries have about 240 clones each and they are not all different?---At that point, we had that number.

When you say "at that point", at the time the work was done?---Yes. I can mention now that we of course have a number that is substantially higher, without having identified EPO cDNA.

Is that work reported in your affidavits?---No, it's not.

As we discussed earlier, there are about 10,000 to 30,000 different messenger RNAs in each cell. You have to say something?---Yes.

Only because it is on the transcript?---There would be a huge overlap between libraries from different - it will not be that one particular cell expressed 30,000 that can be found in one library and then another cell type will express a different set of 30,000, which can then be found in the library from that tissue and so on. There will be a huge overlap of course as the number of human cDNA genes are somewhat limited.

In some of the tissues that you used you wouldn't expect any erythropoietin to be produced at all, would you, like foetal kidney?---Probably not.

Certainly you would agree with me that erythropoietin is not expected to be an abundant messenger RNA?---Certainly not.

I showed you the formula earlier in the Sambrook or Maniatis 1989 document

that they provide a formula for determining how many clones from a library not enriched for lower abundancy messenger RNAs must be screened to have a significant probability of finding a low abundancy messenger RNA, and I pointed out to you that their estimate was that in order to have a 99 per cent chance of finding the cDNA clone of interest, you need to have to screen 170,000 clones?---You mean in that particular library?

That's right?---When you then shift your analysis to different libraries, you will of course get a picture that is different and that is why we tried to analyse as many libraries as possible, because the expression pattern of each gene is of course different from cell type to cell type. So the idea is not to find in the beginning a specific tissue that expressed that gene of interest, but rather to make a comprehensive analysis of gene expression in the human body by taking as many tissue samples you can get and generate cDNA libraries from them and then do a mass analysis by EST sequencing.

We are only talking about fragments of cDNA, aren't we; partial cDNAs? ---Yes.

Included in those libraries are tissues that you wouldn't even expect to be producing erythropoietin?---You could not expect it to be produced from what is known in the literature. But it is interesting to note that from the data that are in the public EST data base, the ones we have looked at actually comes from a library where it would not be expected to be found. So we tried not to restrict our analysis to simply look at libraries where it is expected to be found, because I think this is an example of something that turned out to be somewhat more complicated than you would expect it to be.

So you used a random selection of libraries?---It was not random, it was an effort to cover as much as possible of the human tissues and organs and cell types.

Did you follow up the brain result you got and try to get erythropoietin from the brain library?---It was EST that was deposited in the public data bases, it was not something that was found at HGS and because it was then public available, we did not follow up on it.

So the answer is no?---Yes.

Do each of the libraries that you sighted have at least 170,000 clones?---It varies. There are libraries that do not have that.

You would agree with me, would you not, that on the mathematics if you need 170,000 for 99 per cent probability, that if you only screened, for example, 25,650 clones, you would only have a 50 per cent probability?---Again, this calculation is based on a single library.

In any one library?---Yes. What we are doing is something that is different. We

are analysing hundreds of libraries.

Yes, including libraries that you would not expect to have any expressed erythropoietin?---But apparently at least one of them did express it, because we found it. It was found in the public data base in a library from brain.

Are you saying, Dr Olsen, "Look, I've taken a library from a tissue that I would never expect to express erythropoietin and I am really surprised that I didn't find it"? Is that what you're saying?---I don't know - - -

If you go into a library where you would never expect to have expressed erythropoietin, it is not surprising, if you go into that library, that you don't find it?---No, it is not surprising compared to if you have some knowledge based on, for example, the scientific literature. Then you wouldn't be surprised, of course. What does happen is you get surprised when you actually find it in a library or in a tissue where you would not expect it.

But you can't be surprised if you don't find something that isn't there?---No, that's correct.

HIS HONOUR: That book, we will make that exhibit 4, "Molecular Cloning Laboratory Manual", 2nd Edition, and I don't think I marked Dr Olsen's affidavit as an exhibit, so exhibit H will be the affidavit of Dr Olsen affirmed 27 October 1997. Exhibit J is the affidavit of the same witness, 22 April.

DR BENNETT: I think my learned friend thinks it should be exhibit 5, but I am not keeping track of that at this stage and I'll leave that to you.

MR CAINE: I think Dr Lin's notebooks were 4, your Honour, according to my note.

HIS HONOUR: That was G.

EXHIBIT #4 - "MOLECULAR CLONING LABORATORY MANUAL", 2ND EDITION

EXHIBIT #H - AFFIDAVIT OF DR OLSEN AFFIRMED 27/10/1997

EXHIBIT #J - AFFIDAVIT OF DR OLSEN AFFIRMED 22/4/1998

DR BENNETT: You keep referring to the fact that you identified part of the EPO gene in the public data base that came from brain and another from foetal liver; is that right?---Yes.

Does that indicate to you that erythropoietin might be expressed in more tissues than was expected in 1985 or 1983?---It indicates that EPO seems to be expressed in at least two tissues: one is brain; one is the foetal liver.

And they were the two that you identified using your - - -?---They are in the public EST data base. We did not identify them.

You found them when you screened?---They are available in the public data base, yes.

If a person was wanting to find an erythropoietin cDNA, however, wouldn't it be sensible or reasonable for that person to search thoroughly, libraries in which the gene is expressed rather than canvassing libraries not known to express it?---If you for sure know where a gene is expressed, that would be correct.

Is it a goal of HGS to identify new genes?---Yes, it is.

Erythropoietin is not a new gene?---There may be, for example, alternative forms of it, spliced forms, which we would be very interested in.

You are aware that erythropoietin is said to be a single copy gene?---Yes.

Have you succeeded in finding an erythropoietin cDNA?---No, we have not.

Did you find an erythropoietin-like cDNA?---No, we have not.

Is that program still current?---It is.

Are you in charge of that program?---No.

Are you involved in the program?---I am involved in it, yes. Every scientist in HGS is involved in that.

Have you found any spliced forms of erythropoietin?---We have not found a cDNA that encodes erythropoietin, so no, we have not found a spliced form of it either.

You did in fact twice identify an erythropoietin cDNA which are the two examples you have given, one in brain and one in foetal liver?---No, we did not find them. They were found by others and deposited into the public data base.

I see. So is it the case that if somebody else had already cloned the gene at HGS you didn't particularly want to find it, because you were looking at novel genes?---We would not be interested in particularly the same form of it. What we would be very interested in, for example, would be alternative spliced variants of the proteins, which, in this case, it is not unlikely to be able to find.

You certainly didn't go into, as we said before, libraries made from transfected cells?---No, we did not. We sequenced libraries that are made from normal natural sources like tissue samples and organ samples.

If you found two in the non-coding region, how do you know if it's

mis-spliced?---We don't. You cannot. The question is somewhat unclear.

It is fair to say, isn't it, that you couldn't know if something has been mis-spliced if what you found was a hit in the non-coding region?---That is absolutely correct.

When you did your PCR work, did you check the primers to see if they were liable to be bad primers?---No, we did not. We did not have a specific control available for that experiment with EPO cDNA.

It is the case, is it not, that with primers used for PCR, sometimes those primers simply are bad primers and don't work?---We followed the standard protocol we have in the company for making primers, which include quality control of the amount synthesised and the amount you obtain after the synthesis. So we followed standard protocol for quality assurance.

Your standard protocol does not go to the design of the probe itself, does it?---No, it does not.

DR BENNETT: Your Honour, in view of the complexity of this evidence, from my perspective, I don't know if I have any more questions, but might I just have a short adjournment?

HIS HONOUR: Certainly. Let my associate know when you are ready

ADJOURNED **[3.37 pm]**

RESUMED **[3.44 pm]**

DR BENNETT: How many different clones were there in each of the libraries that you attempted to screen using PCR?---I can't give you that number for sure, but it must have been at least over half a million.

In each of the libraries?---It was in each of the libraries - - -

How much different clones do you say that there were in each of the libraries that you attempted to screen using PCR?---I can't remember that number, but it is huge, it is in the hundreds of thousands.

Do you know that as a fact?---I do not know it for a fact for each and every library.

You say it is worth noting that both of the two EST clones that you obtained were partial sequences and that neither of them contained any of the EPO gene reading frame coding for the erythropoietin protein. That is in fact what you would expect, wouldn't it, that you would get partial sequences?—When you sequence an EST - when you sequence a cDNA clone and get an EST, you get out a partial sequence of that cDNA clone.

You referred to two hits that you obtained in brain and foetal liver. You would agree with me, would you not, that a worker in the art, knowing where those hits were made, could obtain those cDNA clones from those libraries and use them to obtain full length sequences?---Not necessarily obtaining full length sequences. For that, you of course need to obtain a cDNA clone that contains the sequence from the extreme 5 prime end to the 3 prime end.

You could go back into the library where those hits were obtained and use that information to obtain a full length cDNA clone?---Not if it's not there.

We are talking about the original library?---Yes.

If you went back into the original library?---You get a piece of, for example, 3 prime sequence of that particular gene, cannot make you sure of the fact that you will be able to find a clone that contains also the 5 prime end and the coding region.

Let's start with that first. You could go into the library that you searched and get more information from that library, the original library, and get more information on the sequence from that?---The question is somewhat confusing. You can take that cDNA you have now identified and sequence that in full.

Yes?---What you want to do next then is of course obtain a clone that contains the full sequence.

And you could go in, for example - - -?---And you could use the library and the tissue it came from as a source. That would be a place where you certainly would look for it.

And you - - -?---But it cannot, with any certainty, you cannot be sure that you can actually obtain a full length sequence from that particular library or tissue.

No, but you could use that sequence to go into the original tissue source, as you said?---Yes, you could certainly do that.

And you would expect to obtain, using normal methods then, the full length cDNA sequence?---You would hope to obtain the full length sequence, yes.

DR BENNETT: Thank you. Nothing further in cross-examination, your Honour.

MR CAINE: No questions in re-examination, your Honour.

HIS HONOUR: Thank you, Dr Olsen, you are excused

<THE WITNESS WITHDREW **[3.47 pm]**

MR CAINE: Your Honour, the position we are at is my learned friend is to be commended, we have a credit of some 16 minutes. Dr Molloy is the next witness and he will be available first thing tomorrow morning.

HIS HONOUR: How long would he take?

DR BENNETT: Certainly we would hope to finish with him tomorrow. I can tell your Honour that if that is the case, we are a day ahead of what one of our original estimates was in terms of the witnesses. Although, if I do finish with Mr Molloy during the day, the next witness will be Dr John Mattick. So perhaps it may be we will get to him tomorrow.

HIS HONOUR: What volumes are those in?

DR BENNETT: I don't have them to hand. I think there are a number of affidavits of Dr Mattick's, including a primer.

HIS HONOUR: Molloy is 5.

DR BENNETT: Molloy is 5 and Mattick is volume 18, your Honour. Your Honour will see there are three affidavits in volume 18.

HIS HONOUR: Thank you very much.

MR CAINE: There was one matter just before your Honour leaves the bench. My friend and I weren't in conflict over this, but neither of us were certain about the order of final addresses. We might ask your Honour, I suppose, who your Honour would expect to address first.

Obviously, your Honour, if I am cross-examining a number of my learned friend's witnesses deep into the 3 week period, it would influence the extent to which I could prepare written submissions and the like. It helps my friend and I understand the time we would need to properly present the matter to your Honour at the end of the day.

HIS HONOUR: Ordinarily, if you take the analogy of the witness action, the party in the position of the defendant would address first.

MR CAINE: Yes, your Honour.

HIS HONOUR: Which would mean Dr Bennett.

DR BENNETT: Your Honour, we are happy to go first and then go into reply. The only difficulty we have is we are not certain precisely what issues my friend is running and not running. While we have no problem at all in going first, perhaps what we can get from our learned friend is, without submissions, to identify in effect what, in the notice of opposition, he is pressing. Normally of course in the Patent Office, the opponent addresses first because it is the

opponent's onus to establish, if it can, that the patent shouldn't proceed to grant. So we are happy to go first. That is not a problem and I understand the practicalities of that, but rather than be wasting everyone's time, hours and probably, more importantly, the court's in shadowboxing, if we were going to go first, what we would be looking for is just a series of the issues that are still alive.

HIS HONOUR: It is something that concerns me. I wonder whether perhaps by the end of this week at the latest the parties ought to attempt to agree on just an outline of the issues both legal and factual.

DR BENNETT: We are happy to agree on that. I think that will be proffered by my friend first, because it is what he is relying upon.

MR CAINE: Your Honour, I opened the matter in a somewhat more lengthy way than would might normally expect in a matter and I am happy to adhere to the outline of opening. It is a fairly comprehensive document. If my friend says she is uncertain about an area when she is on her feet, she might leave it until reply.

HIS HONOUR: That is fine. If there is any that you don't press - - -

MR CAINE: I will let my friend know, your Honour.

HIS HONOUR: As soon as possible.

DR BENNETT: Just to clarify, sorry to do it through your Honour, what we are talking about are the matters that are set forth in my learned friend's written opening?

HIS HONOUR: Yes. You could, I suggest, elaborate it by descending to a further level of identifying the evidentiary issues which arise in the case.

MR CAINE: Yes, your Honour.

HIS HONOUR: For example, there might be issues that arise from Dr Olsen's evidence and they might be slotted into the structure and you can identify where the particular factual conflict is.

MR CAINE: I think that will require very little extra work, your Honour.

HIS HONOUR: If we make reasonable progress, it would be desirable to leave a gap between the end of the evidence and the submissions, to give the parties a little bit of breathing space.

MR CAINE: I think it would help everyone's digestion of the matter, your Honour, if that were possible.

HIS HONOUR: I am thinking of at least a day or so.

DR BENNETT: I am sorry to raise the matter again, and I know that we are still a way away from the end of next week, but if the matter were not to be completed at the end of the third week, if there was maybe a day or whatever it is of submissions to go, can your Honour indicate at all at this stage which day of the following week - would it be Monday, for example, that your Honour would want to have the matter continue to give your Honour as much writing time as possible in the week, or would it be some other day in that week?

HIS HONOUR: I think it couldn't be Monday or Thursday, it would have to be Tuesday or Wednesday.

DR BENNETT: If the court pleases.

MATTER ADJOURNED AT 4.02 PM UNTIL TUESDAY, 12 MAY 1998

Exhibit List

Genetics 11/5/98

Exhibit No.	Date	Description	Page No.
EXH E	07/08/96	- AFFIDAVIT AFFIRMED BY ANTON HASELBECK 7/8/1996	311
EXH F	03/07/97	- AFFIDAVIT AFFIRMED BY ANTON HASELBECK 3/7/1997	311
EXH 3		- BUNDLE OF PUBLICATIONS BY DR HASELBECK	314
EXH G		- COPIES FROM DR LIN'S NOTEBOOK PAGES 350, 352 AND 355	350
EXH 4		- "MOLECULAR CLONING LABORATORY MANUAL", 2ND EDITION	365
EXH H	27/10/97	- AFFIDAVIT OF DR OLSEN AFFIRMED 27/10/1997	365
EXH J	22/04/98	- AFFIDAVIT OF DR OLSEN AFFIRMED 22/4/1998	365

Witness List

Genetics 11/5/98

AM 67 024621
CONFIDENTIAL

AM-ITC 00809358