UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

IN RE RECOMBINANT DNA TECHNOLOGY PATENT AND CONTRACT LITIGATION	)	
	)	MDL Docket No. 912
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA	)	
Plaintiff,	)	**CAUSE NO. IP 92-224-C D/G**
-vs-	)	Indianapolis, Indiana
	)	August 24, 1995
ELI LILLY AND COMPANY,	)	Afternoon Session
Defendant.	)	

Before the

HONORABLE S. HUGH DILLIN

TRANSCRIPT OF PROCEEDINGS AT TRIAL

APPEARANCES:

For the Plaintiff:	Arthur I. Neustadt Jean-Paul Lavalleye Marc R. Labgold William J. Healey Amy Levinson Kevin Bell Susan B. Tabler
For the Defendant:	Donald R. Dunner Charles E. Lipsey Amy E. Hamilton John C. Jenkins Jeffrey Karceski
Court Reporter:	Patricia A. Cline, CM Antonette Thompson, RPR-CSR

PROCEEDINGS TAKEN BY MACHINE SHORTHAND
COMPUTER-AIDED TRANSCRIPT

(Call to order of the Court at 3:55 p.m.)

PLAINTIFF'S WITNESS, AXEL ULLRICH, SWORN

DIRECT EXAMINATION

BY MR. LABGOLD:

Q. Dr. Ullrich, could you please state your full name for the record.

A. My name is Axel Ullrich.

Q. Could you spell your last name for the record.

A. U-L-L-R-I-C-H.

Q. Would you give your current address.

A. You want my German address or my American address?

Q. Your German --

A. I have two residences. I have a permanent residence in the United States. My address is 70 Palmer Lane, in Portola Valley, California 94028; and my German address is Munich, Adalbertstrasse 108, A-D-A-L-B-E-R-T-S-T-R-A-S-S-E 108.

Q. Will you please tell us what your current position is?

A. My current position in Germany is Director of the Department of Microbiology at the Max-Planck Institute Biochemistry in Martinsried, M-A-R-T-I-N-S-R-I-E-D. This is small town near Munich.

Q. And when did you start at the Max-Planck Institute?

A. I started in December of 1988.

Q. And were you hired as a director?

A. I was hired as a director, yes.

Q. Are you involved in scientific research?

A. I am involved in research in molecular biology and cell biology including research in the area of diabetes and cancer mainly.

Q. Have you published your research in scientific journals?

A. I have published articles in a variety of international journals, and I have more than 300 publications.

Q. Do you have any other current positions?

A. I am also Founder and Chief Scientist of Sugen Corporation, which is a publicly held company in California. This company is also involved in translating the research done in my laboratory and that of my partner, Professor Schlessinger of New York University in the area of cancer and diabetes.

Q. Do you do any teaching?

A. I am mainly teaching by giving lectures, but also by having graduate students in my laboratory, currently more than 20 graduate students.

Q. Do you serve on any scientific advisory boards?

A. I am scientific advisor for the Wistar Institute, the Hagedorn Research Institute, an institute in Denmark involved in diabetes research. These are the main advisory functions.

Q. Do you serve on any editorial boards?
A. I'm serving on a number of editorial boards, including that of the European Journal of Molecular Biology, Cancer Research Journal, International Journal in the United States.
Q. Have you received any awards for your work in research?
A. I have received awards based on my work in the diabetes field from the German Diabetes Association, and in the area of cancer by the French Cancer Society and by American societies.
Q. Could you briefly review your education starting with your undergraduate degree?
A. I was an undergraduate in Tubingen, the University of Tubingen in Germany. Then I obtained my Ph.D. in Molecular Genetics at the University of Heidelberg. Following that in 1975 I moved to the United States and became a postdoctoral fellow at the University of California in the laboratory of Professor Howard Goodman.
Q. Back with your Ph.D., what was the nature of your research that you did on your doctoral thesis?
A. The research was concerned with genetic systems, viral systems at that time before the cloning technology was available. Viruses for very suitable systems to study genetics. And I was studying the transcription translation of certain genes on a variety of prokaryotic and eukaryotic

virus.

Q. Did you receive a postdoctoral fellowship when you went to the University of California?

A. Yes. I received a fellowship from the German research organization, the DFG.

Q. And was that money used to fund part of your research?

A. That funded three years of my research at U.C.S.F.

Q. When you went to the University of California at San Francisco, did you specifically go to work in the lab of Dr. Goodman?

A. Yes. I went to Dr. Goodman's laboratory who was at that time one of the leading researchers, and I should say a number of laboratories in U.C.S.F. were leading in the area of the newly emerging research in genetics and the recombinant DNA technology, as it's commonly called.

Q. What type of research was it that you wanted to perform in going to the University of California, San Francisco?

A. I was very interested in the molecular basis of human disease, and I had already initiated work in that direction in the area of diabetes in Germany, and came then to San Francisco and expressed my desire to work on insulin and the isolation of the insulin -- cDNA and the insulin gene. And that was very much in the interest of Dr. Goodman. And because of the environment at U.C.S.F. at that time, it was also a very appropriate project.

Q. Why were you interested in working in insulin?
A. As I said, at that time the field of recombinant DNA research was in its early stages. And one of the more challenging projects, because of its significance for human disease, was the elucidation of the complete structure of the insulin gene.

And there was history to that because in many of the technological advances in the past, insulin was always in the forefront, the first target for that, for new research possibilities. And therefore, I was very interested also to focus on insulin and to continue then in that direction. So it's the possible development of treatments, of alternative treatments for the diabetes disease.
Q. Now, I think you have said that you arrived at the University of California, San Francisco, I'll refer to that as U.C.S.F., in 1975?
A. Yes.
Q. And so at that time in 1975 you were interested in doing insulin directed research?
A. I was interested in that. But at that time one has to understand the technology was not that far advanced, and it was a very risky project; so therefore, I was engaged in an alternative for a parallel project related to yeast.
Q. You used the term "risky project." What do you mean by the term "a risky project"?

A. As I said, the technology that was necessary to clone cDNA, specific cDNA for a specific gene, was not really that highly developed. At that time methods necessary for this type of project at various stages, including the isolation of messenger RNA in an intact form, the reverse transcription of the messenger RNA, the cloning, the insertion into plasmids; all of this was known more or less theoretically and had been carried out in sort of model systems. But the cloning of the cDNA had not been done in the late 1975 period. Then towards the end of 1975, the first cloning of the cDNA was reported, the cloning of rabbit globin gene by the group of Bennhard Mach and collaborators.

Q. Now, before we proceed into the nature of the work you actually did, I made a note that you talked about the insulin cDNA and the insulin gene. Could you differentiate between the projects that you worked on in that regard?

A. Initially, obviously it was cloning of the cDNA. Isolation of the specific insulin gene proceeded then after these probes were available and were then carried out after I moved also to Genentech at the end of my tenure at U.C.S.F.

Q. For the clarity of the Court to clarify the record, what is the difference when you use the term "cDNA" and the term "gene"? Would you explain the difference between

those two?

A. The cDNA is a copy of the messenger RNA that is found in the cell. The gene is very frequently in a sloppy way also -- or the cDNA is frequently called the cDNA, which is formally not correct because the gene is the stretch of DNA in the genomic DNA. In the nucleus of each cell of our bodies, that contains two copies of all the genetic information, and that compromises our development and life functions. And one stretch of that is that encoding the gene or the protein of insulin or proinsulin or preproinsulin. So that's formally the gene.

CDNA is a copy of the transcript of the blueprint of that gene. That is not a perfect copy of that. It's a processed copy because so-called introns have been excised by specific enzymes. And the messenger RNA that results is then in vitro translated using a specific enzyme into the complementary DNA called cDNA.

Q. Thank you. We'll get into more detail along the way for clarity of the record.

Now, when did you actually begin doing work on the insulin DNA?

A. In the fall, late 1975.

Q. And what kind of work were you involved in in that regard?

A. Initially the problem was isolation of the messenger

RNA from the pancreas of an animal that was suitable. And the problem was that the pancreas produces many enzymes, including high levels of so-called RNase, an enzyme that digests RNA. And obviously you want to isolate from the tissue RNA that is intact. When you have plenty of RNase around, that is not very favorable; and therefore, various ways were explored how one could generate intact messenger RNA.

One of them was to go to an animal that does not produce much RNAs, and that is the dog. So I spent much time isolating messenger RNA and translating this RNA protein from dogs. These efforts lasted a substantial part of 1976. The same time kind of techniques for reverse transcription of RNA were tested. All these were new techniques that had been carried out before in a few laboratories in the world and had to be established in our laboratory.

Q. Was the dog cloning work successful? Were you able to isolate --

A. Excuse me?

Q. Were you able to isolate insulin genes from the dog?

A. No.

Q. Do you have any understanding as to why those experiments were not successful?

A. In that particular case because of the characteristics

of the dog pancreas, which is a solid organ, the sheer number of additional messenger RNAs, in addition to that encoding, the insulin or preproinsulin messenger RNA, diluted this RNA so much that it became at that time essentially impossible to clone the dog cDNA.

And therefore, we ultimately decided then in a collaborative effort with members of Bill Rutter's group to first isolate from rat tissues of the islets of Langerhans from rat pancreas. That contained or had been shown to contain high levels of messenger RNA for insulin, preproinsulin.

Q. So once you decided that the rat was the animal that you were going to proceed with, you mentioned the islets of Langerhans. Can you describe how this relates to the pancreas?

A. The pancreas is an organ that produces -- that has two major functions. There's an exocrine pancreas that produces all the enzymes that digests our food, enzymes that break down proteins in DNA and RNA. And then there is the endocrine pancreas. Anatomically this can be distinguished very nicely. This has been shown that these so-called islets can be identified under the microscope, actually visually even when one isolates the rat pancreas, see these islets, and they have been discovered by Langerhans, a scientist in the last century.

And because of the differences in the tissue composition of these, the endocrine and the exocrine pancreas, it is possible to separate these tissues. This technique was worked out and perfected by John Chirgwin and Bill Rutter.

Q. Why was it the islets of Langerhans that you were proceeding after?

A. Pardon? I didn't understand.

Q. Why were you seeking to isolate the islets of Langerhans?

A. Because these islets of Langerhans are the cell types in our body that produce insulin. Therefore, the prediction was that they will contain large amounts of messenger RNA for preproinsulin. And by isolating these specific mini organs they would not be diluted or the messenger RNA for preproinsulin would not be diluted by the huge amount of messenger RNA coding for digestive enzymes in the exocrine pancreas.

Q. And was one rat pancreas sufficient for your purposes?

A. No. It was necessary to sacrifice a large number of rats. As a matter of fact, in a very brute force effort, we isolated islets from 200 rats and successfully isolated the amount that we thought was sufficient to isolate the necessary amount of RNA, subsequently messenger RNA, subsequently cDNA, for our planned cloning experiments.

Q. You mentioned the work of John Chirgwin. In what regard, how did that play into this isolation?
A. The cooperation that we were engaged in was perfect in that there were expertises in that laboratory relating to the isolation of the islets and isolation of messenger RNA from tissues that contain high levels of RNase. And that's one technique that John Chirgwin had worked on for quite a while and perfected. And I used some of that technique for later experiments for the isolation of RNA from the islets.
Q. Have you continued to use that technique that John Chirgwin developed in your subsequent research?
A. Well, I combined the technique developed by John Chirgwin with another technique that facilitated the isolation of RNA made with a very straightforward and safe procedure. And this technique is now being used in many laboratories still today, I would say.
Q. Now, in your work on the rat, was mRNA isolated?
A. From the tissue isolated from these 200 rat pancreases, I was able to isolate 1 milligram approximately of total RNA, including ribosome RNA, and from that about 50 micrograms of so-called poly-A plus RNA, which comprises the messenger RNA fraction of the RNA in the cell.
Q. And what did you use the RNA for?
A. This RNA or fractions of this RNA were initially used for preliminary experiments, analytical experiments, to

test the quality and suitability of the RNA for subsequent experiments. And then from about 40 percent, 40, 50 percent of the RNA, cDNA was prepared for subsequent cloning experiments.

Q. And how was the quality and suitability of your RNA project?

A. In this critical experiment I would say everything worked perfectly. The RNA was of high quality. The cDNA generated was expert quality. You can see that from our publication. You can judge that by looking at the size of the cDNA that you generate. And the yield in terms of amount was also very good.

Q. Was the cDNA that you prepared, was it sufficient for more than one experiment?

A. It was clearly sufficient for more experiments. I used only a part of the cDNA for subsequent steps.

Q. And when you say "subsequent steps," what was in the next step that you took with your cDNA?

A. Next step was treatment of the cDNA with an enzyme called S1 exonuclease which served to generate as many of the messenger RNA molecules as possible, blunt ended, so they would be suitable for the attachment again in an enzymatic step using an enzyme called ligase, DNA ligase. Using this enzyme to attach synthetically, generate it, DNA linkers to the ends of the cDNA.

Q. And we've heard the term "linkers," and I'm sure we'll hear it again. Would you briefly describe what the function of a linker is?

A. One critical aspect of cloning on recombinant DNA technology in general was the discovery and characterization, isolation of so-called restriction enzymes; enzymes that specifically cut DNA at certain places; specific sequences where it recognized the specific enzymes and cut in a specific way.

And this was possible then, or this knowledge allowed us then to synthesize such recognition sites for enzymes and attach these synthetic linkers to DNA that digested the enzyme, and generate ends of the DNA, of the synthetically generated cDNA now, that would allow us to insert these DNAs into the cloning vectors, the plasmid.

Q. Now, were you aware of the existence of the NIH guidelines at that time?

A. Yes, of course.

Q. And did the cDNA preparation that you described, was that covered by the NIH guidelines?

A. No.

Q. Did you attempt to follow those guidelines?

A. Yes, of course.

Q. And did you take subsequent steps which were covered by the NIH guidelines?

A. Yes. As soon as DNA is introduced, at that time, was introduced into living organisms, into microbial organisms, at that point the guidelines govern everything that you do. And obviously everybody in the laboratory followed those guidelines.

Q. Did you attempt to clone your cDNA?

A. Yes, I did.

Q. And which vector did you use for that cloning?

A. In the first attempt I used the vector pBR322.

Q. Did you believe it was okay to use that under the guidelines?

A. Yes, I was convinced that it was okay to use this vector because we were, for quite a time, waiting for the approval of that vector for use under the guidelines. And I obtained with all my reagents ready to go to the next step, the cloning step. I obtained a phone call from Mary Betlach, who was a technician in Herb Boyer's laboratory, and she had spoken with him, with Herb Boyer, who was a member of the RAC committee who attended a meeting in Miami where the NIH Recombinant DNA Committee had a session to decide about the suitability of pBR322 for use in cloning experiments. She had told me on the phone that the committee had approved the use of the vector.

Q. And have you subsequently learned otherwise?

A. No.

Q. Why was it Herb Boyer's lab that you were looking to with regard to these vectors?
A. Herb Boyer's laboratory was very active in the development of cloning vectors at that time.
Q. And did they, in fact, develop this plasmid that you referred as to pBR322?
A. They developed this plasmid pBR322 and others.
Q. Now, when you heard from Mary Betlach that the plasmid had been approved, what did you do next?
A. I went ahead and did the experiment, the cloning experiment, meaning transformation of bacteria, of the appropriate bacteria strain, and selection on the appropriate agar plates, and then subsequently characterization of the clones.
Q. Now, when you did the cloning, did you have to do it in a special facility?
A. Yes. This had to be done in the so-called P3 facility.
Q. Could you briefly describe what a P3 facility is?
A. P3 facility is a laboratory that contains all equipment necessary for the execution of such cloning experiments under conditions that would not allow the escape of bacteria from the laboratory. In other words, there was negative pressure in the laboratory and there was an autoclave in the laboratory that would allow us to destroy all bacteria, all living organisms containing potentially

dangerous DNA in this laboratory. So no bacteria that were transformed by plasmids containing exogenous DNA could be transferred to the outside world.

Q. Was the P3 lab required under the NIH guidelines?

A. Yes. For this type of experiment, yes.

Q. You do your experiments in that lab?

A. Yes.

Q. And did you do them in that lab in accordance with the guidelines?

A. Excuse me?

Q. Did you do them in that lab because of the guidelines?

A. Yes.

Q. Okay, was there a P3 logbook?

A. At that time, these were the first experiments and we didn't have the logbook right at the beginning. This was introduced somewhat later.

Q. Now, did you need approval to use this P3 lab?

A. Yes.

Q. And who was that approval obtained from?

A. Well, it was supposed to be the head of the laboratory. And at that time Dr. Goodman was in sabbatical, so I don't recall exactly who gave the approval. But first either the representative of Goodman in the laboratory or a member of the recombinant DNA committee that was first supervising these activities.

Q. And did you seek approval for all of your experiments to be done in the P3 lab?

A. Yes.

Q. Now, did you subsequently learn that pBR322 had not been certified?

A. Yes, later I learned -- actually, first from Herb Boyer, if I remember correctly, that the plasmid was approved but not certified, a distinction that I did not really, I was not aware of the bureaucratic procedure that was involved in bringing the plasmid actually to the public, to the general use for scientists. And I have to say I was not the only one who did not understand that, who was not aware of this very all-important distinction.

Q. You did wait until the plasmid was approved before proceeding?

A. Yes.

Q. Now, you subsequently learned that the plasmid was not certified?

A. That's right.

Q. How did you come to learn that it was not certified?

A. It was after the conference that, in Utah, that I attended, Miami that Howard attended. We obtained a phone call from John Shine who told us that one of the clones, definitely of the ones that I had obtained, contained plasmid including cDNA that encoded part of preproinsulin.

We were very excited about that. And then after returning from that class which, I think, coincided with Herb Boyers' return from Miami and things sort of came together. My excitement and my report to my colleagues that my experiments had been successful.

And I assume also John Shine's reports to others raised that issue. Herb Boyer heard about this and told us then that yeah, it's approved but not certified, so we may have a problem here.

Q. Now John Shine you mentioned, what was his role in these experiments?

A. John Shine was the one in the laboratory who had established and worked out the DNA sequencing procedure which had been developed in the laboratory of Professor Gilbert, and was at that time still in its infancy and not used in too many laboratories in the world so he was the one who sequenced the clone DNA.

Q. When you say he was the one?

A. He.

Q. Who was the "he"?

A. John Shine.

Q. Was he proficient in DNA sequencing?

A. He was an expert at that time as much as I was able to judge.

Q. Was there anybody else around who was a better

sequencer than John Shine?

A. No.

Q. Okay. After it was determined the cloning had proceeded in an approved but uncertified vector, what steps were taken next?

A. There were meetings and discussions of -- very intense discussions -- and ultimately, many of the things that were going on that Howard Goodman and Bill Rutter were involved in as heads of the laboratory and the department respectively, I was not really fully familiar with and aware of. But eventually the decision was made to destroy the clones that were obtained in that experiment.

Q. And what did you do with the clones?

A. One morning I came in the lab and took my clones and put all the tubes into a beaker and poured acid on them which leads to the destruction of DNA.

Q. Did you keep any of the biological materials which were --

A. No.

Q. -- derived from pBR322?

A. No.

Q. So all of the fruits of your experiments, they were put to what end?

A. Yes.

Q. You destroyed them?

A. They were destroyed, yes.
Q. Okay. What was -- what did you do next?
A. Well, again, as a result of further discussions, we decided to use the material that we still had, the cDNA that I knew was of high quality. And there was also still RNA left. And wait or use alternatives for the cloning, including plasmids that were approved. For example, pCR1 at that time, or wait for approval of another plasmid that would be probably more practical and more promising than pCR1 is.
Q. And I believe you had referred to earlier that there was still cDNA from the original preparation?
A. That's correct, yes.
Q. And this was the cDNA which you were going proceed with?
A. Yes.
Q. Now, then that cDNA was that prepared in accordance with the NIH guidelines?
A. Yes.
Q. I think you may have said the NIH guidelines, did they govern the preparation of that cDNA?
A. No, of course not.
Q. So did a plasmid, suitable plasmid, for your needs become available?
A. Eventually the plasmid pMB9 became certified and pMB9

is a sister plasmid of pBR322, already the name says pMB. "MB" stands for Mary Betlach, who is the technician who gave me the information about the approval of pBR322. So she had or she was a key person developing this plasmid.

The other plasmid, pBR322, is named after two post-docs, Bolivar and Rodriguez, also in Herb Boyer's lab.

So there were related plasmids that used the same or partly the same genetic elements from other plasmids that were put together and tailored to sort of usable size and with very advantageous characteristics.

Q. Now, did you proceed to clone with pMB9?

A. Yes, we decided to use pMB9 and essentially the cDNA that was still available was still of good quality, was modified with linkers as before, and used in a perfectly analogous experiment as with pBR322. And that experiment, that cloning experiment was also successful.

Q. Did you wait to clone pMB9 until it was approved and certified?

A. Yes, until after it was certified.

Q. Now, did you have any contact with the NIH?

A. I recall that I, during the waiting period after the pBR322 information had reached us that it was not certified, we were all very anxious and especially I was eager to continue with my experiments. And I called at one time the office of Dr. Gartland who is the head of the

recombinant DNA committee of the NIH and inquired about the status of approval and certification for the plasimds of 322 and pMB9.

Q. Were your pMB9 experiments successful?

A. Yes.

Q. And what were the, what further experimentation were the pMB9 clones subjected to?

A. The standard experiments followed. The isolation of plasmids and characterization of the plasmids. At that time, we were very much, you know, in a hurry to get these experiments done very quickly because we were, we had been delayed by this unfortunate misunderstanding before.

And at that time John Shine was putting all his effort into characterizing these plasmids that were obtained, the clones that were obtained in my cloning experiments.

Q. Now, at this time and in the preceding periods, could you describe briefly what your working habits were, type of hours you kept, et cetera?

A. Well, my working habits were rather intense and sometimes erratic. I lived very close to the University, about one block away from U.C.S.F., Parnassus Avenue and because of the intensity of the situation, I frequently woke up at midnight and went to work at 2 o'clock or things like that.

But this was not only at that time. I still have these

habits now. So this is more not so much circumstantial, but personal characteristics. So I worked at all times of the day and night.

Q. Were there other in the lab who kept similar types of hours?

A. Oh, yeah, at that time Peter Seeburg and John Shine and others occasionally work also at strange hours. Definitely in the department there was almost around the clock, always somebody somewhere.

Q. You never closed. Now did, were the cloning experiments successful?

A. Yes.

Q. And you isolated DNA which encoded --

A. Plasmids with inserts, actually the experiment with pMB9, I used different fraction cDNAs that were treated in various ways and some preparations, the yield of clones was even better than with pBR322.

Q. Who did the sequencing on those experiments?

A. John Shine did the sequencing.

Q. Was there anybody else who assisted John in the sequencing experiments that you know of?

A. Not that I recall at this time.

Q. Did you publish the work in a scientific journal?

A. Yes, the work was published in the Journal of Science.

Q. And I'd like to refer to what we have marked as

Plaintiff's Exhibit 98. And it will be in that black book that's in front of you there. Just to confirm, is this the report of your work?

A. Yes.

Q. Was this work reported here based on pMB9?

A. Yes.

Q. Was the experimental data that you reported here based on pMB9?

A. The data that I generated, yes. And the sequences were generated by John Shine. So, yes, referred to him.

Q. Did you also file a patent application based on your pMB9 experimentation?

A. The University of California filed the patent application.

Q. And I'd like to refer you to the next exhibit which is PX2, we have come to know as the '525 patent. Is that patent the patent based on your pMB9 experiments?

A. That's what I understand.

Q. Now, were there any people or research groups who were interested in your rat proinsulin cDNA clones?

A. Yes. This work generated a lot of interest. Not only by scientists, but also by the general public because it was recognized that this was the first step towards the development of a new way of treating diabetics and made that first critical step towards the isolation of

corresponding human sequences and the production of human insulin in bacteria.

Among these, among those that were interested were a number of pharmaceutical companies that were active in the insulin and diabetes field. This included Eli Lilly, but also others. For example, the German company Hoechst.

Q. Now, were you aware of a collaboration which developed with Eli Lilly & Company?

A. Excuse me?

Q. Were you aware of a collaboration which developed with Eli Lilly & Company?

A. That collaboration developed, yes, subsequent to the successful experiments.

Q. And did you have an understanding as to whether Eli Lilly & Company was interested in those rat clones?

A. Oh, definitely. They were very interested and the clones were made available to Eli Lilly as far as I understand.

Q. Why didn't you work on humans at that point in time?

A. At that time, the NIH guidelines did not allow experimentation with genetic material isolated from human tissues or cells except in high-security facilities that were called P4.

In the United States, as far as I remember, there was only one such facility, therefore, it was essentially

impossible to do the experiments with human material.
Q. Why didn't you just clone the human cDNA in a P3 facility?
A. That would have been against the NIH guidelines.
Q. Did you, during the collaboration with Lilly, did you have any personal involvement with any of the individuals at Eli Lilly?
A. Later on in 19, late 1977 and then especially in 1978, yes.
Q. What happened in 1978?
A. In 1978 after the collaboration with Eli Lilly was formally established, the next goal was obviously to clone the human preproinsulin cDNA. And as I just said, the NIH guidelines did not allow to do this under P3 containment conditions. And therefore, possibilities to do these experiments nevertheless were discussed and lead to the establishment of a P3-like laboratory in France within the facilities of a Eli Lilly-owned subsidiary or actually plant of Lilly where normally only perfume was produced in France near Strassburg.
Q. Whose idea was it to use this Lilly facility for this purpose?
A. I don't know whose idea that was.
Q. And why was it France that this facility was going to be?

A. The guidelines in France that governed recombinant DNA research were somewhat more relaxed at that time than those in the United States. They allowed experimentation with human material in facilities that were essentially equivalent to our P3 facilities and therefore could be built within a relatively short period.

I think it took Eli Lilly to build this laboratory in France only about three months. The equipment and the whole set up was essentially the same as our P3 facility in San Francisco, but it allowed us to do experiments which we were at that time not allowed to do in the United States.

Q. And the purpose of these experiments was to achieve?

A. To achieve the goal of cloning human sequences and coding preproinsulin before this was possible in the United States. But the ultimate goal was to, as quickly as possible, get the sequences and make them available for the development of bacteria producing insulin by Eli Lilly.

Q. Did you know why Eli Lilly wanted to produce insulin by recombinant means?

MR. LIPSEY: Objection to the form, hearsay. Calls for --

A. It was an obvious --

THE COURT: Overruled. Go ahead.

A. The reason is pretty obvious. The insulin market in the world is divided among, essentially, among three large

companies or two major. It's a Danish company at that time Novo, now Novo Nordisk, and Eli Lilly & Company and getting to the goal to have bacteria, genetically engineered bacteria organisms, that produce insulin or proinsulin would be a major competitive advantage because the sources that were traditionally used for the isolation of insulin essential for the treatment of diabetes, namely the pancreas tissues from cattle and from pigs, were slowly diminishing.

There were predictions that these sources would disappear or at least would not be sufficient to fulfill the needs for these people who suffer this disease. But of course, also the possibility to produce human insulin rather than cattle or pig insulin was a major, was considered to be a major competitive advantage. And therefore, Eli Lilly was very interested in using all possibilities to get to that goal as quickly as possible.

Q. And did you have an understanding that Lilly wanted a proinsulin DNA?

A. They were very interested in our work and our work was aimed at the isolation of human proinsulin, cDNA.

Q. Did you go to France?

A. Excuse me?

Q. Did you go to France?

A. I went to France, yes.

Q. Did you work in the Lilly facility?
A. Yes, during the second half of 1978, from August on essentially until late October, I spent several time periods working in that laboratory and carrying out cloning experiments that were analogous to those I had varied are carried out in San Francisco on rat material.
Q. Was anybody with you in France?
A. Yeah, the guidelines in France specified that experiments could not be carried out by one researcher alone. There had to be a witness present that had also to countersign the logbook that was necessary in that laboratory. And from the very beginning my first partner if I may say so was an employee of Eli Lilly, Dr. Paul Burnett.
Q. Did he aid you in any of these experiments?
A. Not really. He was just watching me; he was present. This was not only for control reasons, but also for safety reasons, just in case that I faint and something happens that would require assistance. So he was there and he countersigned the entries in the logbook and in my notebook at that time.
Q. Were there any other Lilly employees that were there during the time you were?
A. Yeah, I think somebody named Dr. John Sharp was also later on present.

Q. Did you understand at the time whether these people were employees of Eli Lilly & Company?

A. Yes, I knew that they were employees.

Q. Now, were you successful in cloning human insulin?

A. I was successful in obtaining clones from a human insulinoma, messenger RNA, cDNA from that. And several clones were characterized and demonstrated later on in San Francisco to contain, represent partial sequences of human preproinsulin.

Unfortunately, at that time I had decided to leave U.C.S.F. and accept the position at Genentech. And therefore, I left U.C.S.F. before the work with my clones was completed.

Q. Did you pursue insulin cloning after you went to Genentech?

A. Yes. Then after I had joined Genentech in 1979, one of my projects was also the cloning of human, full-length cDNA and coding.

Q. Now, were you aware of any experiments regarding hamster insulin cloning?

A. Yes, at that time, it was already after the rat experiments were successful, and our collaboration with Lilly had been established. John Sharp, in Paul Burnett's laboratory was engaged in experiments attempting to clone the cDNA coding hamster insulin with the goal in mind to

modify that cDNA to generate human insulin, sequences -- I mean sequences encoding human insulin.

Q. So you assisted him in that cloning?

A. He had serious problems and I assisted him and later on also carried out experiments in France with cDNA generated from hamster material.

Q. Now just to have you review this couple documents which we've marked as Plaintiff's Exhibit 152, do you recognize the handwriting on that document?

A. Yes. This is my handwriting.

Q. Do you have an understanding as to who the "John" referred to here is?

A. Yes, this was John Sharp.

Q. Did this relate in any way to the experiments that were being done in France?

A. Yes. It is obvious that this is a letter I wrote to John who was at that time in France and I asked him to, because he was a scientist and more engaged in laboratory work than Paul Burnett, he was able to assist me in some of my experiments there.

Q. If I could have you look briefly at Plaintiff's Exhibit 153, and do you recognize that document?

A. Yes, this is my handwriting.

Q. And do you have an understanding as to who the "John" reference there is?

A. This is, without any doubt, John Sharp.
Q. And did this also relate to any work that you did in France at the Lilly facility?
A. Yes, it is obvious that this is related to that work.
Q. I would like to offer into evidence Plaintiff's Exhibit 152, Plaintiff's Exhibit 153, and also Plaintiff's Exhibit 544 which we haven't reviewed. That's Dr. Ullrich's CV.
MR. LIPSEY: No objection, Your Honor.
THE COURT: The three exhibits mentioned will each be received in evidence.
(Plaintiff's Exhibit(s) 152, 153, 154 received in evidence.)
MR. NEUSTADT: Thank you, I have no further questions.
MR. LIPSEY: Your Honor, may I proceed?
THE COURT: Yes, go ahead.

CROSS-EXAMINATION

BY MR. LIPSEY:

Q. As a preliminary matter, Dr. Ullrich, Plaintiff's Exhibit 153 you just said related to work that you did in France; is that right?
A. That's what I believe, yes.
Q. And that work you said was done in 1978, right?
A. Yeah.
Q. And this letter has a date on the bottom March 16,

1979; is that right?
A. That's not my handwriting and it's impossible that -- I was not engaged in this kind of work in 1979, at least not in connection with anybody named John.
Q. There are a couple of preliminary matters and I apologize if I repeat. You are employed by the Max-Planck Institute in Munich right now, is that right?
A. That's correct.
Q. And you had previously been employed by Genentech from about January 1, 1979, to about June 30, 1988; is that right?
A. That's correct.
Q. And you had been employed at the University of California from approximately October of 1975 until January of 1979; is that right?
A. It depends how you define "employment."
Q. You were working there, right?
A. I was working there. I had a fellowship from the German government for a large part of that time. And I was, obviously, still a German citizen.
Q. I hate to do this to you at six minutes to five, but I'm going to give you a big book. Unless, I am happy to start it, if the Court would like, I am happy to --
THE COURT: Well, if you're unhappy to give that to him, why don't we wait and give it to him in the

morning?

MR. LIPSEY: Sounds fine to me, Your Honor.

THE COURT: All right. We'll be in adjourned until 9 o'clock tomorrow morning.

(Court adjourned at 4:55 p.m.)

INDEX OF PLAINTIFF'S EXHIBITS

EXHIBIT NOS.	RECEIVED	NOT RECEIVED
287	613	
5	620	
537B, 537C, 537D, 537E, 537F, 537G	633	
537A, 537H through 537P	645	
434	667	
78 (pages 03-119 through 03-122)	674	
328	760	
152, 153, 154	815	

INDEX OF DEFENDANT'S EXHIBITS

EXHIBIT NOS.	RECEIVED	NOT RECEIVED
3205A	613	
3065A, 3037A, 3087	615	
3126	667	
3124, 3015, 3140, 3139, 3142, 3143, 3144	744	
3509	775	
3280	777	
3757	779	

INDEX OF EXAMINATION

PLAINTIFF'S WITNESSES	DX	CX	RD	RC	RDC	RCC
JOHN H. RICHARDS	615	678	744	747		
KATE H. MURASHIGE	748	759	779	781		
AXEL ULLRICH	784	815				