Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

Axel Ullrich, Ph.D.
MOLECULAR BIOLOGIST AT UCSF AND GENENTECH

An Interview Conducted by
Sally Hughes
in 1994 and 2003

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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It is recommended that this oral history be cited as follows:

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Axel Ullrich, 2001

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Genesis of the Program in Bioscience and Biotechnology Studies

In 1996 The Bancroft Library launched the forerunner of the Program in Bioscience and Biotechnology Studies. The Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. Yet, although the university is located next to the greatest concentration of biotechnology companies in the world, the Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as the Library's new director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences and generates constant public interest and controversy is vital for a proper understanding of science and business in the late twentieth and early twenty-first centuries.

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history, archival, and Internet program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management and to digitalize documents for presentation on the Web in the California Digital Library. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in Bioscience and Biotechnology Studies was given great impetus by Genentech’s major pledge to support documentation of the biotechnology industry. Thanks to these generous gifts, the Bancroft is building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in

primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library networks; and, in most cases, digital presentation at http://bancroft.berkeley.edu/ROHO/projects/biosci.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
November 2005

October 2005

ORAL HISTORIES ON BIOTECHNOLOGY

Program in Bioscience and Biotechnology Studies
Regional Oral History Office, The Bancroft Library
University of California, Berkeley

Richard Scheller, Ph.D., *Conducting Research in Academia, Directing Research at Genentech*, 2002

Robert A. Swanson, *Co-founder, CEO, and Chairman of Genentech, 1976-1996*, 2001

Axel Ullrich, Ph. D., *Molecular Biologist at UCSF and Genentech,* 2006

Daniel G. Yansura, *Senior Scientist at Genentech*, 2002

Oral histories in process:

Brook Byers
Ronald Cape
Stanley N. Cohen
Donald Glaser
James Gower
William Green
Keiichi Itakura
Irving Johnson
Daniel E. Koshland, Jr.
Arthur Levinson
Arthur Riggs
Stephen Rosenberg
William J. Rutter, volume II
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto
William D. Young

INTERVIEW HISTORY—Axel Ullrich

The two interviews contained in this volume largely reflect two episodes in the multifaceted and accomplished career of Axel Ullrich. The first interview, conducted in 1994, centers around his years (1975-1977) as a postdoctoral fellow in the Department of Biochemistry and Biophysics at UCSF and the two controversies that roiled out of his research on human insulin. One involved an alleged violation of the just-emerging National Institutes of Health Guidelines for Recombinant DNA Research at a time of political turmoil over the safety of such research. Ullrich describes his role in the turmoil and the effort of his department and the School of Medicine to contain the political fallout. The second episode, a source of subsequent litigation between UCSF and Genentech, centered around his decision to leave the university and join Genentech in 1979. He discusses the allegation that he and Peter Seeburg, also a former UCSF postdoc, took laboratory materials to Genentech which the university claimed as its property. Other oral histories in the Genentech series, as well as those with William J. Rutter, chairman of UCSF biochemistry at the time, also provide perspectives.

The second interview, conducted in 2003, nine years after the first, focuses on his career at Genentech and touches on his later accomplishments. By employing Ullrich and Seeburg in 1979, Genentech gained capacity in an alternative approach to genetic engineering using complementary DNA. The company had learned that DNA synthesis, applied in its earlier successes with the cloning of somatostatin and human insulin genes, was not an optimal method for cloning larger genes, such as those for growth hormone and the interferons. By hiring the two former postdocs, Genentech sought to cover both methodological bases. Ullrich describes his work on human insulin and even more notable research on growth factors. A basic scientist at heart, his accomplishments were not fully appreciated by the corporate hierarchy with its focus on product and profit. Frustrated by Genentech's failure to follow up on his research on the gene HER-2, which he and collaborators found to be related to an oncogene, Ullrich left the company in 1988 and joined the Max Planck Institute for Biochemistry in Germany. Later work, by Ullrich and others, on a monoclonal antibody to HER-2 eventually led to Genentech's famously successful Herceptin, a treatment for breast cancer. With Joseph Schlessinger in 1991, he co-founded Sugen, Inc., a company focused on signal transduction therapy and later went on to form two other companies. In yet another career change—"a new adventure," as he described it--Ullrich recently moved to Singapore to become Research Director of the OncoGenome Laboratory of the Centre for Molecular Medicine.

The first interview was conducted at Sugen in Redwood City, California, and the second in a San Francisco hotel room, following Ullrich's trip to Saudi Arabia to receive the 2003 King Faisal International Prize for his work on breast cancer. Aside from overviews of Ullrich's research contributions and the contested state of basic research in commercial biotechnology, this oral history provides striking evidence, if more indeed is needed, that science is anything but an ivory tower occupation; that the interactions between it and the wider society are inevitable, sometimes contentious, and often politically and legally consequential.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is under the direction of Richard Cándida Smith, and the administrative direction of Charles B. Faulhaber, The James D. Hart Director of The Bancroft Library, University of California, Berkeley.

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Historian of Science
Regional Oral History Office
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December 2005

[Note to the reader: Section I was recorded on March 12, 2003 but moved here for better chronology.]

[Interview #2 March 12, 2003]
Begin Tape 5, Side A] ##[1]

I. FAMILY BACKGROUND AND EDUCATION

Family Displacement in World War II

Hughes: Tell me a bit about your parents, and your growing up years and education.

Ullrich: My parents are from a region in the northern part of Czechoslovakia, which traditionally was once a mixed population of Germans and Czechs, so-called Sudetenland. My father was of German origin and my mother was a Czech. I was born towards the end of the war, not in that region but across the mountains in a region called Schlesen or Silesia. But my parents lived there only for a short time because my father was in the army and then the war began. I actually don't know why they moved to a place called Lauban. So that's where I was born, almost sixty years ago, on October 19, 1943.

That was a critical time when the Russian army approached, and my mother had to leave there. She wanted to go home to where her parents lived, to Sudetenland, Czechoslovakia, which at that time of course was part of the German Reich. The first critical moment in my life could have abruptly ended because my mother had to go through Dresden. She was right there on the day when the big bombing attack took place. My brother was four and a half years older than me, and I was a little over one year old. We were right there in the middle of the city that was burning and bombs were falling. I don't remember that, of course, but my brother was five or six years old, so he remembers.

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[1] ## This symbol indicates that a tape segment has begun or ended.

We were lucky and made it safely back into Czechoslovakia, which then when the war ended closed the borders. My brother went to a Czech school. My first language was Czech. So there was my mother with two boys, and my father was a prisoner of war in northern Germany in a British prisoner of war camp. So this [situation continued] until ’48 when I was about four and a half years old. There was a last chance for my parents to get together. Because my father was in the German army, they considered it not a good thing that he would come back to Czechoslovakia. So my mother decided to leave Czechoslovakia and go to Germany with us. We arrived in Germany in ’48. I didn’t speak any German and my brother didn’t either. This is where my first memories sort of start--the long train ride through Germany and the ruins. But we adjusted very quickly. I forgot my Czech and learned German within three months. I ended up in a small town called Rastatt near the border to France.

Hughes: Why there?

Ullrich: My aunt and uncle and their two children had moved there. My father had joined them, and that’s why we went there, too. A nice small town. It was in the so-called French zone because Germany was divided into zones. That’s why I didn’t learn English; I learned French in school, and that’s where it all began. I liked living there. My parents had a very tough time. They had lost everything. They had absolutely nothing. There was this so-called Wehrungsreforme, the reform of the monetary system after the war. The former currency was being used, but the new currency, the German mark, was established. Everybody, every adult and every child, I think, received forty German marks, and that was the basis of our existence. My father had no real profession because due to the war he had to--

[End Tape 5, Side A] ##
[Begin Tape 5, Side B]

Ullrich: --poor. It was amazing. My mother found a job because she spoke Czech, and she used to be a secretary in a lawyer’s office. So she found a job at a mission of the Czech government which was near [?] in Baden-Baden. I remember in winter, it was really cold. We had this small apartment which was very cold because we didn’t have enough money to buy coal. So she came sometimes from her job and had in her purse one piece of coal, to heat all night. Amazing. We were very poor but my parents were determined.

This time after the war was really amazing--all these energies were activated in people who lost everything, material things. There were some programs where you could buy very cheaply houses. They bought a small house and established sort of a grocery store which my mother was running. My father was working in the city administration. So they made a living for the four of us, and they were always very determined that we get a good education. I didn’t want to go to high school. All my friends were carpenters and blacksmith sons and so on. So I

wanted to stay with them in the regular schools. But [my parents] convinced me that I should go to high school, so I did.

Hughes: On the university track?

Ullrich: Yes. I had a very nice childhood and my parents were very good. It was exciting. We lived on the very edge of the town. There was a big garrison of French soldiers there which had their training grounds right behind our house. So it was very exciting to watch, to hang out there. I had already developed a very keen interest in everything that lived--animals, plants. I was exploring all these little ponds created by the bombs that had fallen there, so water had accumulated there. There were all these interesting animals, insects, and frogs and stuff. So, this [interest in biology] was already there, very early. And that was also my favorite subject in school, and so I was always good in biology or chemistry. Not so good in mathematics or literature or whatever. I was always sort of an average student but succeeded to get the final certificate which allowed me to go to a university. There was never any doubt what I would do. There was this new subject, biochemistry. I never wanted to become a teacher because I always had trouble with teachers because I was a very troublesome child, just like later.

Hughes: There is a theme here. [laughter]

Ullrich: Absolutely. So, I heard about this new curriculum, biochemistry, which was only possible to study at one university, in Tubingen, and so I went to Tubingen.

Hughes: And I think that's where we pick up with the earlier interview.

[Interview 1: April 4, 1994]
[Begin Tape 1, Side A]
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II. THE DEPARTMENT OF BIOCHEMISTRY, UC SAN FRANCISCO

Decision to Leave Germany

Hughes: Well, Dr. Ullrich:, I think the place to start is with Germany and how you got the idea of coming to this country and what you intended to do when you got here

Ullrich: Well, that's very simple. I didn't speak any English; I did not learn English in school. I learned French and Latin. Then I became a biochemist and it was clear that I had to speak this language, so that was one of the incentives. The major one was, a postdoc usually went to the United States from Germany. It still is the

case, but there was at that time absolutely no question. So I had to do that, and I wanted to learn English and at the same time I wanted to be in an exciting part of the country. So it was California. I applied to labs in San Diego and in the Bay Area. The news about this new promising [recombinant DNA] technology reached German laboratories. In '75, Herb Boyer came to our lab and gave a seminar.

Hughes: Which was where?

Ullrich: In Heidelberg at the molecular genetics department at the university. Herb Boyer gave a talk about restriction enzymes, and then I met this young Ph.D. student, Peter Seeburg, who went to university with me in Tübingen. We both went there because that was at that time the only place in Germany where we could study biochemistry. There was no other place.

Hughes: Really?

Ullrich: Yes, in '75. You could study chemistry and then focus on the biochemical side of it. [But] an actual curriculum for biochemistry existed at that time only in Tübingen. So both Peter Seeburg and I went to that university. And then I went to get a Ph.D. at Heidelberg in the Department of Molecular Genetics. Peter Seeburg's Ph.D. advisor, Heinz Schaller, was also appointed professor in Heidelberg. Peter was almost finished. I met him and he told me he was going to Herb Boyer as a post-doc. So, then I told him that I was also applying to labs in the San Francisco area and that it sounded very interesting.

I applied to Mike Bishop [at UCSF] and I was turned down. He said he didn't have any space. And I knew Herb Boyer's lab was full, so I didn't even apply there. I didn't know Bill Rutter at that time. In all the papers that Herb Boyer published at that time, there was Howard Goodman as co-author. I was told by Herb Boyer that he and Howard had a joint grant and they were collaborating very closely. So I thought that would be a very good lab to apply to, and I did, and I was accepted, and I got a fellowship.

Hughes: And that was 1976?

Ullrich: '75. October 17th, I left [Germany].

The Reaction in Germany to Recombinant DNA

Hughes: 1975 was the year of the Asilomar Conference [on Recombinant DNA Molecules]. Had any of the concerns about recombinant DNA appeared in Germany?

Ullrich: Not yet. Germany's always about ten years behind what's going on here. But I remember at that time already in the popular press you could read articles as a consequence of the Asilomar meeting and the resulting publicity. I remember one article in a magazine like Time or Life [in which] they predicted that they could produce hormones in bacteria and all these things, even though at that time nothing had actually been done. It was pure speculation. Even until early '78 it was still speculation. Everything was laboratory scale and academic. Nobody really knew whether this [technology was] going to pan out [commercially]. Who knew whether the bacteria or whatever other organisms would not recognize these proteins and degrade them? Actually, I was quite convinced that this [degradation] would be happening. I was quite skeptical that all this would work.

Arrival in Howard Goodman's Lab

Choosing a Research Project

Nevertheless, I thought, if I go off [to the States], it should be [to] something real important.

Hughes: But you hadn't come with a research project in mind?

Ullrich: Well, I had actually started to do some work in Germany already along these lines. I worked for my thesis on the question of whether one could translate messenger RNA from one organism, on ribosomes, or in cell-free translation systems of other organisms. I tried to translate messenger RNA from bacteria or from bacteriophages in mammalian cell-free translation systems, and vice-versa. For example, I translated rabbit messenger RNA on E. coli ribosomes, and prokaryotic RNA in mammalian translation systems.

I started with a friend, Stephan Peter, who was a physician and worked in an anatomy lab at the University of Heidelberg. I started to extract RNA from chicken pancreas because in chickens the pancreas is subdivided into sections. One section produces mostly glucagon RNA or glucagon protein and another part produces insulin. I tried to make RNA and translate that, and I had already thought of doing something in the area of insulin. Something important. I always wanted to do something medically important. And that's when I arrived in San Francisco.

[Howard Goodman and I] talked about projects. He wanted me to work on some esoteric yeast project. I thought, well, I would really want to do some cDNA [complementary DNA] cloning. Nobody had cloned any cDNA at that time. That was in '75.

Hughes: Nobody anywhere?

Ullrich: Well, actually yes. DNA sequencing was not even invented yet. The first paper on cDNA cloning appeared in December '75.

Hughes: Was it an obvious thing for you to think to do?

Ullrich: It was extremely risky. I was just stupid. [laughter] I really didn't know what I was doing and what I was aiming at. I had no idea.

Hughes: What was Dr. Goodman's reaction?

Ullrich: Well, he thought, oh, yes, this sounds rather risky. Then we sort of agreed that we would try both [projects]. I was really not interested in that yeast thing that I started along these lines. Then I started talking to Jerry Grodsky. Somebody connected me with him, and I think it may have even been John Baxter. But I had the desire to do something that was important.

I was, to some extent, also influenced by Peter Seeburg, who had arrived [at UCSF] half a year before me. He worked on growth hormone very, very closely with John Baxter. So he had this sponsor in John, who was extremely enthusiastic, in contrast to Goodman who was extremely pessimistic and skeptical about everything.

Hughes: Was that his nature or was he truly skeptical about your specific project?

Ullrich: No, that was his nature. He was a very negative person.

Hughes: So you had not much support?

Ullrich: I had essentially no support at all. I had picked this most risky project. At the beginning I didn't know that Bill Rutter was involved in pancreas development research and that he had actually somebody there in his lab [working in that area]. There was very little communication. Somehow Howard Goodman was sort of an outcast in that department.

Hughes: Based on what?

Ullrich: Based on his personality. He was just a very, very strange guy. He never had any graduate students in all these years because they all disliked him. [He is] one of these people who probably means well but has a very, very negative aura. So the

people in his lab were outcasts by association. Howard especially disliked Bill Rutter, I guess because Bill had many of the qualities that Howard just didn't have. [Bill was] very smooth and very, very talented and [had] political skills--all these things that Howard didn't have. Therefore, there was no communication.

Competing with the Head of the Department

I didn't really know what I was getting into. I think we were in a different building. I think we were in HSE [Health Sciences East] and they were in HSW [Health Sciences West]. And then this episode described in Stephen Hall's book [occurred].[2] Jerry Grodsky started to support me and sponsor me a little bit because he was the insulin/diabetes person in the Metabolic Research Unit of the university. Then Don Steiner came who was one of the big names in the world in the field of insulin and proinsulin at that time. And he gave [a talk on] translation of pre-proinsulin messenger RNA in a cell-free system. After the talk, Jerry Grodsky introduced me and said, "This is [Axel] Ullrich:; he wants to clone insulin." And there was Bill Rutter introducing John Chirgwin and saying the same thing. [laughter]

Afterwards, we met in the elevator and Bill said, "We have to talk." And then Howard and I were essentially ordered into Bill's office and told, "If anybody in this department clones insulin, it's either in my lab or in collaboration with me." I don't know how Bill operated otherwise, but he clearly knew what was important. And he used his power in such cases even though he does not appear to be such a person. I have never seen him in any other situation where he has said, "Okay, this is how it's going to be." The first thing that happened, unfortunately, was he essentially booted Jerry Grodsky out of the whole picture.

Hughes: On what grounds?

Ullrich: Well, there was no space for Jerry. I don't know if there was anything between them or not; I don't think so.[3] For me it was a loss because, as I said, Peter had found a sponsor in John Baxter on the medically oriented side for the growth hormone project, and I really didn't have anyone. Clearly, what turned out then to happen was a more-or-less controlled competition rather than a cooperation, at least for the first year, until the end of '76. So we divided things up. I was doing dog pancreas. John Chirgwin was trying to do rat pancreas. And we both didn't make much progress.

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[2] The episode, which Ullrich goes on to describe in the next paragraph, is also recounted in: Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene*, Redmond, WA:Tempus Books, 1987.

Rutter & Goodman Labs Cooperate to Compete with Wally Gilbert

But then this news came about competition from the East Coast. I think it was in May or June of 1976. There was some Eli Lilly-sponsored conference in Indianapolis where they had invited different people working in the insulin field. They had also invited Howard Goodman, and I think Bill Rutter was there. Somebody named [William] Chick reported that an insulinoma tumor that he had established to grow in nude mice or in rats could be transplanted and that he was in the process of also establishing cell cultures. That was, of course, a major advantage in regard to cloning insulin cDNA. The next thing we heard was that he was in Boston and tied up in a collaboration with Wally Gilbert. And that, of course, scared us all.

Hughes: There were a few things stacked against you.

Ullrich: Oh, yes!

Hughes: You were competing with the chairman of the department and Wally Gilbert.

Ullrich: And I was competing in our own lab. I was essentially fighting against Howard Goodman who constantly wanted to stop this [project]. "This will never work. No, no, no." Fortunately, he went on sabbatical in Japan in September '76. So he was far away. From that point on, things started to look better because he also was extremely stingy with buying reagents. For example, we needed radioactive substances for our experiments and he wouldn't allow us to order them. By nature, he was extremely negative, and therefore he always said, "No, no, that won't work so we won't even try." He was the opposite of me. I said, "First let's try and let's worry about the results later."

Goodman left and that was for both Peter and me a blessing. From that point on, things started to look very good. Until then, there was not much of a

[3] For Rutter's viewpoint, see: William J. Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco," volume 1, an oral history conducted in 1992 by Sally Smith Hughes:, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998..

collaboration. Essentially, the threat from the outside was what brought us together and really turned the competition into a collaboration.

Hughes: The two laboratories were Rutter's and Goodman's?

Ullrich: Yes.

Obtaining Islet Cells from Rat Pancreas

Hughes: Well, what did that mean for you?

Ullrich: Well, it meant that we really started to talk, and to talk about strategies and about joining forces, and about the focus that all of us would pursue. That would be John Chirgwin, Raymond Pictet, and me. We decided, since we didn't have any insulinoma, at least not the rat insulinoma--We couldn't work with human material at that time. That was not allowed by the NIH. So we had to go after the isolation of pancreatic islets, the tissue that produces insulin. So that's what we did. That decision was born out of the competition with Wally Gilbert because we had heard the Chick story and all these rumors that things were really going well over there [in Boston]. Only later we knew they had similar problems. They put some guy on, Forrest Fuller, who blew the whole thing for them. But for us that misinformation was clearly a great advantage.

Hughes: It wasn't a psychological hurdle to have to deal with the animal material? Was that fairly routine for you to handle?

Ullrich: The animal experimentation issue is really problematic. It grew in maybe the last five to ten years. Of course, what we did was not for any frivolous reason. It was completely a very, very important need that we were pursuing. We had to kill two hundred rats, and it was done very professionally. So that was really the important step.

We joined forces and made the decision to isolate those islets. As a result, I had this test tube, and there was this pellet in the bottom, very white. The pellet was the islet tissue from two hundred rats. And then it was my responsibility to make RNA, which is still a problem today. Very sensitive, very difficult. This was one of the most stressful experiments I ever did.

Hughes: Ullrich:Was the technology there?

Oh, sure. Well, the technology to some extent had been developed by John Chirgwin, and then I had improved the method to isolate intact RNA. I used that method and it worked perfectly. In that case, it made beautiful RNA. I reverse

transcribed it and it was just perfect. Sometimes these things happen. Once it has to work, everything works.

Hughes: Was the Gilbert group taking a similar approach?

Ullrich: Well, no, they used this rat insulinoma. But they probably didn't have the RNA isolation procedure. They failed on every level--it's amazing. It can also happen the other way around: It has to work, but nothing works. They had a great advantage: they had so much tissue, and it was tissue that could be regenerated. It was renewable material. For us to go through another two hundred rats was not something that we were looking forward to. If I messed up the whole thing, then four people had to start working all over again.

Hughes: Did you feel the tension?

Ullrich: Of course.

Hughes: What kind of hours were you working?

Ullrich: Crazy hours. I'm always an early-morning person. Sometimes when I couldn't sleep because of all of the stress and tension, I got up at two o'clock and went to the lab. I lived right in the next block from UC[SF] and Parnassus [Avenue]. I was in the lab at four or five o'clock in the morning. But then, I didn't work late at night.

The Rutter Lab

Hughes: Was there a lot of frenzied activity? What about William Rutter's lab?

Ullrich: Well, Rutter's lab was always quiet. This is one of the things about Bill Rutter that I never understood: At that time at least there were very few really outstanding people coming through his lab. He was clearly able also to get good things out of people who were pretty average, so that speaks for him really.

Hughes: How do explain that?

Ullrich: He didn't really have at that time a reputation in the molecular biology field. Definitely not. He was more into the development of the pancreas, ribosomal RNA later on--nothing really that exciting. Yet he had a big flow of people coming from Chile to Pablo Valenzuela, et cetera.[4] But, otherwise, he had lots of average people. Graeme Bell is one of the people who came to be very successful after he left his lab. But not many big names came out of his lab.

Hughes: Was it the insulin cloning that established Dr. Rutter's reputation in molecular biology?

Ullrich: Well, it took quite a while until he caught up with the other labs. I think most of the credit for the insulin cloning went initially to Howard Goodman. Definitely. But Bill Rutter somehow made more out of it, a lot more than Howard Goodman. And that's something about him I really admire. His lab had to catch up because they didn't have all the necessary techniques established. They were at least a year or two behind all the other labs in that department. And people like Graeme Bell were the ones that got the whole thing going.

Hughes: Yet I have gotten the impression that Dr. Rutter was generally anxious to seize the latest technology and make sure that it was used in the department.

Ullrich: Yes, he clearly had the foresight, so he hired the right people. It's really amazing. He hired assistant professors and higher level scientists; really excellent people. [Tape cuts off]

[End Tape 1, Side A] ##
[Begin Tape 1, Side B]

Ullrich: Bill clearly got more and more involved in our projects, but he had a rather sketchy picture of the whole thing. There is no question that he was not as technically involved or detail-oriented as Howard Goodman. Howard was always into methods and gadgets.

Hughes: When did Dr. Goodman return?

Ullrich: He didn't like it in Japan, so he moved his sabbatical to Seattle in the early part of '77. And then he came occasionally down [to San Francisco.] By then, things were already going well when the famous incident with pBR322 happened.

The pBR322 Episode

A RAC "Approved" vs a "Certified" Plasmid

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4. There is an oral history in progress with Dr. Valenzuela who has a different view of the Rutter lab in which he was a postdoctoral fellow in the 1970s.

Hughes: What effect did the NIH guidelines [for recombinant DNA research] have on your work?

Ullrich: Obviously, we knew about the guidelines and we had the printed guidelines. But the decisions by the RAC [NIH Recombinant DNA Advisory] Committee were not really communicated well. This was all in the process of being established. So it was not like [Donald] Fredrickson or the head of the RAC Committee, [William Gartland] communicated RAC decisions to researchers in the field. [Tape break] Even if Bill or anybody else heard something, they wouldn't come around and tell us. It was all rather improvised. At the establishment of the P3 facility [in the Department of Biochemistry], they tried to establish a committee, but there was no real communication. Very little communication.

Hughes: Whatever communication there was, was it by telephone? Was there written exchange?

Ullrich: If there was anything written I would have never seen it. Probably information went out to faculty members, but they never came down to the postdocs.

Hughes: I remember seeing a letter from Hans Stetten, apologizing to David Martin, who was head of the UCSF Biosafety Committee, about the "collapse of appropriate communications between our Office of Recombinant DNA Affairs and workers at the University of California, San Francisco."[5]

Ullrich: Oh, yes.

Hughes: Martin must have written a letter of protest about RAC's lack of clarity regarding the guidelines. Stetten said that he had asked somebody on RAC to publish a list of certified plasmids. Apparently, there was a lot of confusion about the difference between "approved" and "certified."

Ullrich: Clearly, that [distinction] came up [against] my limited language skills at that time. Clearly, I had no idea there was a difference between "certified" and "approved." And I didn't even <u>think</u> about that. I still have a block against all lawyer language. So I didn't even think twice about it.

There was this situation: I had this RNA; I knew it was reverse transcribing; everything looked beautiful; I was ready to go. I was waiting for the word because, at that time, even though we had no practical experience in cloning cDNA because we couldn't really do it. We thought that pBR322 was better and safer as a cloning vector. Therefore, I wanted to use it. I was no expert in that plasmid stuff, so I just took the word of the guys from Herb Boyer's lab with whom we communicated frequently. This was a unique situation really, the kind

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[5] DeWitt Stetten, Jr. to David W. Martin, June 20, 1977, AR86-7, carton 2, folder 76, Archives and Special Collections, UCSF Library.

of communication that was going on, the interactions and so on. It was clearly different from the rest of the department.

This was a lucky set of circumstances that the right people were together. I wouldn't even give Bill Rutter the credit for that even though somewhere the basis was created by him. But without these people, which include Paco Bolivar and Herb Heyneker in Boyer's lab, John Shine, Peter Seeburg, and myself in Howard Goodman's lab, this would have never happened. It was a magic combination of the right people. You needed people like Bill Rutter to set up things, but then a few crazy postdocs just went for it. Without trying to put Bill Rutter down, there was not anybody in his lab who was comparable. Graeme Bell--he was a graduate student who worked on ribosomal RNA--developed later on into that type of person. And Mary Betlach was also a very important person in this context.

Hughes: According to Stephen Hall, Mary is the one that actually is said to have told you that pBR322 was "approved" rather than "certified."[6]

Ullrich: Yes.

Hughes: And then there was the question of whether you really understood what that meant.

Ullrich: Oh, I didn't even think about that. Mary did not call and say, "Oh, yes. 322 is approved but not certified yet." No, no, no, she did not. This came up later, after the fact, after it happened. I think it was at some kind of meeting after Boyer had returned from Miami, someone said, "Well, it's not really certified yet." And then it started to dawn on me.

Hughes: Well, maybe it was the meeting that was called in connection with the P3 lab and the initiation of the logbook. Remember that?

Ullrich: Yes.

Controversy over a Key Experiment

Hughes: At that time, Boyer very clearly stated that pBR322 was not certified.[7] But you had clones by then, didn't you?

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[6] Hall, p. 116.

Ullrich: Yes, we had clones. And I made no secret that I had done the experiment. And nobody seemed, really, to worry too much about it at the time. Then it was sort of like an avalanche. It started to get bigger and bigger and bigger. Especially from the point on in March '77 when we knew that the clones contained insulin sequences. And then the political stuff in the department started to go on and all these complicated things with individuals and their feelings and personal relationships and all that. Then the lawyers came in. It was unbelievable. They interviewed all these people. I would like to read some of what they said. I'm sure there are lots of things that I don't know.[8]

Hughes: Well, tell me a little about your perceptions.

Ullrich: Well, in Howard Goodman's lab, there were these different factions, people who did exciting cloning and people who did projects that were not so exciting. At least, that's how it was perceived. There was this polarization of strange personalities involved. Janet Manson left Howard's lab around that time because of alleged discrimination or something like that. She couldn't stand it anymore. And Betty Craig, too. They were friends and one of them was pretty friendly with me. It turns out that they were among the first ones to blow the whistle on this.

Hughes: On the plasmid issue?

Ullrich: On the whole thing. Even though this use of the 'wrong' plasmid was never kept secret in any way, they took it one level higher, to the [UCSF biosafety] committee, to make it official. Well, maybe not; [maybe] they only started to talk to some faculty members. A technician in Bill Rutter's lab then finally blew the whistle and took it to Dave Martin, who was the chairman of the [UCSF biosafety] committee. Jennifer Meek was the technician who blew the whistle.

Then things started to move fast and different plans were made: How one should proceed from these documents of the biosafety committee that were written up. That's also described in Stephen Hall's book. A document was written up listing different alternatives about what to do with the insulin clones, [ranging from] destruction of all clones up to keeping the clones because they're not dangerous in DNA form. Everybody, especially Howard and Bill, started to think in legal terms.

Hughes: Legally in reference to the guidelines?

[7] Hall, p. 122.

[8] The reference is to a lawsuit, for which Ullrich and others were deposed, between the University of California and Genentech. The case was eventually settled out of court.

Ullrich: In reference to the guidelines. That's when the communication between Bill Rutter and Stetten started. Bill used him essentially as an advisor about how to proceed. The whole lead was taken over by Bill Rutter. It was this strange thing. Howard was at that point leaving all of the hard stuff to Bill Rutter, but he nevertheless benefited from the paper that was eventually published[9]--much more than Rutter because Howard was last author. But clearly, Bill was the one who mapped out the whole strategy on how to deal with the situation.

Decision to Destroy the Insulin Clones

Hughes: And what was the strategy?

Ullrich: Well, what were our options? Obviously, we didn't want to destroy all the clones, all of this work. We knew what we had was something important. I didn't feel guilty in any way. I hadn't done anything [wrong]. I innocently had done something which in terms of procedure wasn't great, but it was not dangerous. pBR322 was safer than the other plasmids, which was then established by some microbiologists. It was a somehow unreal situation for me. My future, my existence, everything was dependent on this [project].

Hughes: And there was also the competition with the Gilbert group.

Ullrich: Well, we had also done something important which would lead to some important advances in the treatment of an important disease. And just to throw that out of the window, we all didn't like that idea. So, we thought, what do we have to do? That was maybe May, June--or April [1977]? Everything happened within a few weeks. We opted to keep the clones but not put them in bacteria and to destroy all the bacteria, but to keep the clones and to try to finish the sequencing.

Hughes: That was technically no problem? You just snipped out the insulin sequences?

Ullrich: Oh, yes. No problem. But then things started to turn. I guess [due to] pressures from the [biosafety] committee and advice from Stetten that said we can't really do this; we have to destroy the clones. And this happened when Howard was not in the lab; he was in Seattle. At some point, we just decided, we had to do it [destroy the clones]. This coincided with the more public actions through Jennifer Meek. And then there was this unrest in the department. All these people thought this [recombinant research?] was unethical. It was a difficult two,

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[9] DeWitt Stetten, Jr. to David W. Martin, June 20, 1977, AR86-7, carton 2, folder 76, Archives and Special Collections, UCSF Library.

three, four weeks. This culminated in Bill being called to testify to the [U.S.] Senate Subcommitee [on Science, Technology and Space].[10]

Hughes: Which didn't occur until November 1977.

Ullrich: When was the Science article by Nicholas Wade?

Hughes: I have it here.[11]

Ullrich: That was after we published the paper in June.

Hughes: That was September 30th, 1977. So it was after your publication. Boyer and Rutter testified in the Senate in November.

Ullrich: So, much later. Before the paper was submitted, we decided we had to destroy the clones, the DNA and everything.

Hughes: Was that a joint decision?

Ullrich: Yes, that was a decision that was made in the absence of Howard Goodman, but together with Bill Rutter and everybody involved.

Hughes: Did you have to destroy the clones?

Ullrich: Well, I didn't have all the clones. John Shine had some of the clones for sequencing because he was the only one in the lab who knew how to sequence DNA at that time. But I didn't know [if he destroyed his clones?]. I destroyed all the clones that I had.

Hughes: How did that make you feel?

Ullrich: I don't really remember. I just know it was on a Saturday morning. And the lawyers nailed it down by circumstantial evidence to which Saturday it was. The 25th of April or May or something.

Hughes: Were you distressed?

Ullrich: No, I don't think I was very worried about it because the point was that I still had that beautiful RNA and that beautiful cDNA from the rat islets. I had only used half of the cDNA that I had made.

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[10] See: "Testimony Before the Senate Subcommittee on Science, Technology and Space by William J. Rutter, November 8, 1977," draft, William J. Rutter papers, MSS 94-54, carton 2, folder 24, Archives & Special Collections, UCSF Library.

[11] Nicholas Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project," *Science* 1977, 197:1342-1345 (September 30).

Repeating the Key Experiment

Hughes: So you knew you could do the experiment again?

Ullrich: So I was somehow confident that I could do it again with a different plasmid. And that's what I did. So I just took the same cDNA that I had before and used a different plasmid. And it worked, and I got clones, and that's the dispute now. That's where the Lilly lawyers are trying to find some lies or something, some dishonesty in there.

Hughes: Really?

Ullrich: They say they have all kinds of evidence, which we, I think, can all explain. So that's one of their strategies. They don't care about the legal [aspect of] breaking the guidelines fifteen years ago. For them it's a patent issue. You describe in a patent, this is how we did it. But in reality [if] you did the whole thing differently and they can prove it, that invalidates the patent. It's called "the best-mode rule." You have to describe the best mode of operation for reproducing your invention for anybody else. That's the principle in this country. The patent has to be disclosed and anybody should be able to reproduce this [invention].

Hughes: And your opponents maintain that it's not possible according to the patent description?

Ullrich: Well, they say, "You said, you did it in pMB9, but in reality you didn't even destroy these clones. You used your pBR322 and created two clones." And even though I personally cannot swear that there was not somewhere still in the lab a [pMBR322] plasmid--because Howard was so paranoid that he probably kept these plasmids somewhere--I know that I destroyed everything that I had. And we used pMB9. So we'll see. But even though it was clearly a difficult thing for me, I don't remember that I was in a big state of panic.

Hughes: Well, one of the contentions of the Nicholas Wade article is that the experiment went too well, that it was implausible that you could repeat the experiment in roughly three weeks. At the end of that three week period you submitted a paper to Science.

Ullrich: That's one thing that the lawyers are focusing on. Two things in response: First of all, if an experiment works, it works, and it's fast. You can piece things together and next day you have a few clones and you look at them. And by then sequencing was rather fast. Things don't go that fast if the experiments don't work. Then you have to repeat.

Hughes: But they'd already worked.

Ullrich: They had worked with the same procedure, just with a different plasmid. The thing with the paper was a little strange. It's not strange, but it looks a little strange because Howard had already started writing these papers when the pBR322 data were available. So he had already a final draft and just switched plasmids. I have written papers myself in two days. It can be done, no problem. Only retrospectively it looks strange. At that time I was not very involved in writing the paper. Howard and Bill did that.

Hughes: Everything was going on simultaneously is what you're describing?

Ullrich: Yes, essentially. Because of all these pressures, everybody was standing ready to go--John Shine and the sequencing and so on. Because I didn't do any of the sequencing, I don't know whether John still had any fragments from before. All these things, I don't know. That's all in these legal depositions. You probably should have a look.

Hughes: It would be very interesting.

RAC and the UCSF Biosafety Committee

One of the contentions that the UCSF biosafety committee had to deal with was why wasn't RAC immediately notified that the wrong plasmid had been used. The clones were destroyed, but RAC was not--

Ullrich: RAC wasn't notified? Hmmm.

Hughes: That's what the documentation maintains.

Ullrich: I didn't remember that. I thought Gartland was eventually informed.

Hughes: He probably was eventually but--

Ullrich: Not officially.

Hughes: Somebody from RAC wrote to Martin, as head of the biosafety committee, with quite a list of questions on this very issue. One of the questions was, why wasn't RAC informed that the wrong plasmid had been used and that eventually the clones had been destroyed?

Ullrich: I don't know. I have to say, some of these things went by us. Dave Martin never spoke with me. There was also this feeling of resentment, not only [of] me and

other postdocs, but there were all of these things going on that we really didn't know although we were a part of it. It was really strange. And it was, of course, a major issue of discussion.

Peter Duesberg's Opinion

I remember this party once in Jay Levy's lab, and Peter Duesberg was there. I had applied also to his lab. He couldn't accept me because he never opened my application letter. He admitted that to me at that time. He said, "Oh, yes! Your name rings a bell, but I think I never opened your letter." Duesberg was famous for that. [laughter] He just didn't open his mail.

I talked to Duesberg at that party, and I asked him what he would do. I think this was before this whole 322 story started. No, it was probably during this 322 time. I asked him, "What would you do if you had this situation? You have a plasmid you can use and you're not allowed to use it yet." It was around Christmas [1976] when we knew that the plasmid 322 was available, but we couldn't use it yet. It was before the Miami [meeting]

Hughes: Jay Levy traditionally has a Christmas party.

[End Tape 1, Side B] ##
[Begin Tape 2, Side A]

Ullrich: [Duesberg said,] "No question, you <u>have</u> to do it [the cloning experiment]. Don't you worry about it." But I didn't do it. I was afraid to get in trouble. But he was <u>so</u> emphatic: "This is all bureaucracy. Science has to move. This is for a good cause. You have to do it."

There was also an awareness that it was not politically expedient to allow this episode to be widely known and the effort was to contain it. The guidelines were barely in place and they were being violated.

Ullrich: It was an interesting time for me.

<u>UCSF Patent Applications</u>

Hughes: UCSF called a press conference to announce the cloning of the rat insulin gene,[12] and the postdocs felt that they were not given proper credit, particularly you.

Ullrich: Oh, yes.

Hughes: Do you want to comment?

Ullrich: Well, this set up a whole different spectrum of reactions and events because then the whole patent situation emerged, which was a total mess, complete mess, because nobody had dealt with anything like that before. And the growth hormone [gene cloning?] happened about the same time. The lawyers, this guy Lorance Greenlee, was advising UCSF.

Hughes: He was a university attorney?

Ullrich: No, he was an outside person, and he, I guess, was also not certain what to do. So it was the question, who should be an inventor on these patents? And then they said, "Well, it's better to have fewer inventors." First, they wrote patents where they included both growth hormone and insulin and all the people around. And then they divided it up [into two patent applications], and it went back and forth.

Hughes: There's a patent on which you are included as an inventor and there's a patent with only three names, not yours.

Ullrich: Well, then they retracted this [latter] patent [application] and they changed it again. So the patent that is now issued, ten years after it was filed, has my name on it.

The Human Insulin Cloning Project

0In '78 this whole affair with cloning human insulin started, and [UC] contracted [with] Eli Lilly that supported UC and Genentech. And then they built this P3 lab in France, just for the cloning of insulin and for growth hormone.

Hughes: Lilly?

Ullrich: Lilly. They established a P3 lab in France. Got it approved by the French local committees. And their rules [regarding recombinant DNA research] were slightly different than ours, slightly more relaxed than the American rules.

Hughes: Which was the point of moving the research to France.

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12. [Press conference announcement], May 23, 1977, UCSF News Services, William J. Rutter correspondence, carton 6, folder: various press releases.

Ullrich: In America one wasn't, in '78, allowed to do any experiments with human material except in a P4 facility, which was not available to us. In France, it was allowed to do human cloning in P3. So that's why Eli Lilly established a P3 Lab in this small company near Strasbourg, France. And that's where I went. So for half a year, between summer and November of '78, I shuttled back and forth between Strasbourg and San Francisco to clone human insulin.

Hughes: And Wally Gilbert was doing something similar in England.

Ullrich: He re-cloned rat insulin. [laughter] They were totally destroyed at that point.

Hughes: Is it understandable that they would mistakenly clone rat insulin?

Ullrich: Well, it shouldn't have happened. It can happen--it happened to us later.

II. GENENTECH, INC. AND BEYOND

Unrest among the Postdocs

During that year of '78 the whole patent issue became bigger and bigger. I think in October of '78--I was in Strasbourg--I was told by a representative of Lilly that Genentech had beaten us to expressing human insulin in E. coli, that Genentech had cloned the A and B chains and expressed them and gotten activity. So that was that. And then I heard that the lawyers and Goodman and Rutter and [Baxter?] had decided to kick all the postdocs off the patent and have just one patent for growth hormone and insulin, with only the three of them on it [as inventors]. That tipped the balance, and I said, "Okay, forget it." I had had a job offer from Genentech since April of '78 which I had first accepted and then rejected because I really got scared about being the first scientist in a biotech company, not knowing, is this going to work? I actually had that offer longer than that. But I changed my mind. Then Genentech renewed the offer.

Genentech already had some people; they had some success. I said, "Okay, I will now take the job if John Shine and Peter Seeburg would also go." If all three of us would go, I would feel safer. They made an offer to all three of us, and Shine sort of weaseled out of it. Then Peter and I went to Genentech as a consequence of that patent dispute.

Hughes: What was attractive about Genentech? Or was it because of the negative things happening to you at UCSF?

Ullrich: For me, it was clear. I was a postdoc for three and a half years. What was my future? I had a job offer from Germany, [but] I preferred to stay in this area. I liked California; I liked San Francisco and the Bay Area. So I asked Howard and Bill, what can they do for me? And they offered me a position as a non-faculty research assistant in [the UCSF department of] biochemistry which was more or less a continuation of the postdoc tenure. I really wanted to get out of Howard's influence. So nothing really materialized, and I don't know why. But I had this offer from Genentech, and I thought, well, I just want to stay in this area. I didn't think about money; I didn't think about stock. I didn't even understand what stock was.

Hughes: Times have changed.

Ullrich: I still don't know. My decision was based simply on staying here and not going back to Germany.

Hughes: It wasn't the prospect of doing good science?

Ullrich: How could we know what Genentech would be? Essentially, we made it what it is. And that was made out of concern. The reason Genentech became such a major power in basic research is because of people like me and Peter. We were worried that if we started doing commercial research we would have problems returning to academia if things wouldn't work out. We were discriminated against at that time. We thought that if we [did] all this applied stuff, we couldn't publish. It would be terrible. We would never get a job if the company failed. If it turned out that this whole thing would never work, we would be in the streets. So we had to publish. We put pressure on Bob Swanson who didn't like that. We said, "Okay, we have to publish. We have to establish a university-like atmosphere." And that succeeded.

Hughes: That set a precedent, didn't it?

Ullrich: Oh, absolutely. It was a completely new model, which is very, very powerful. [tape break]

Hughes: What was the feeling in the Department of Biochemistry about the commercial ties that were developing in molecular biology?

Ullrich: There was a lot of bad feelings about that [from] people like Keith Yamamoto and Christine Guthrie. There was a lot of antagonism. We felt like outcasts and that generated some energy to make our point. And there were a bunch of very good people at Genentech in the beginning who were critical, really instrumental in getting the whole thing going. It was the right people, at the right time, in the right place. I was very lucky to be part of such events [at] several times.

Offers from Genentech

When we started to think about moves towards expression of human insulin, there was an attempt in '78 when I was still at UCSF [to] join in with Genentech in an effort to include Howard Goodman, even though Howard Goodman had over all this success split up with Herb Boyer. They had fallen out over all this. But then there was this attempt to join forces again--Boyer and us involved in Genentech, even though we would be off-site [at UCSF]. That was then aborted because Bill Rutter intervened because Howard Goodman wanted to do that without Bill Rutter. Howard still didn't like him; they had such different personalities.

But then when Bill Rutter heard that there were attempts to enter formal collaboration with Genentech on the basis of insulin, he intervened and he said, "Well, only if I'm part of this, and I want as many shares as Herb Boyer."[13] And then of course the whole thing fell apart. When I finally decided to join Genentech, I still tried to keep peace with Howard because of all the critical views of him. I still had a certain amount of sympathy for him. So I tried to get him involved, but by that time the atmosphere was so poisoned that nobody wanted him to play a part in Genentech anymore. So that didn't happen. Since that [time], I never talked to Howard again.

Hughes: Really?

Ullrich: Well, I met him once in the airport in Frankfurt, by accident! [laughs] It was very uncomfortable.

Hughes: I don't hear people talking of running into him.

Ullrich: Well, he sort of isolated himself. He more or less disappeared from the stage completely. He moved more into the plant area. I don't know what he's doing now.

One of the tragic and comical sides that happened was that Howard Goodman for his great work in insulin cloning was then awarded this huge amount of money from a German company, Hoechst. For almost twenty years now, they've supported his research. They must have given him in the range of two hundred million dollars, and he never did anything for them. And they never did anything for me or Peter Seeburg. [laughs] One of those mysteries of big business.

Hughes: Well, look what you have now--Sugen.

Ullrich: That's right. It took a long time to get this [company] started.

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[13] For Dr. Rutter's viewpoint, see his oral history.

Later Competitions with Rutter

Hughes: You were drawn back into the competition--

Ullrich: With Bill?

Hughes: Yes.

Ullrich: Well, yes. See, the insulin cloning mapped out certain routes that were more or less obvious to pursue. And my interests developed in the same direction as those of Bill Rutter. So we continued to work in parallel and in the same direction. It was never hostile. Whenever I met Bill at some meetings we were always very friendly. It was clearly competition, especially when it came to the insulin receptor, and we beat him by a month. But years after, it didn't mean anything in terms of our relationship. I would rather have Bill Rutter as a competitor than anybody else. He's a good guy. So that really was not a major problem for me. We both got credit and a lot out of this even though we have reached some of the discoveries or benchmarks or milestones at the same time. Both of us did well. It's not that one destroyed the other.

Hughes: Well, thank you.

[End Tape 2, Side A] ##

[Interview #2: March 12, 2003]
[Begin Tape 3, Side A] ##

II. GENENTECH, INC. AND BEYOND (continued)

Recruitment

Hughes: Dr. Ullrich:, a number of years ago, I guess it's seven to be precise, we talked about your postdoctoral years at UCSF. Today we're starting with your career at Genentech. I believe you arrived there in January 1979. Is that right?

Ullrich: That's right.

Hughes: You talked last time about the negative things that had happened at UCSF, and I wonder if there were some positive things that you felt about going to Genentech.

Ullrich: Oh, certainly there were positive things because my time at UCSF really got my scientific career started. When I first came to this country and to UCSF, I was certainly not the person who was already at that time enthusiastic about science and being a scientist. This happened during the time at UCSF that I matured in that way.

Hughes: Now, were you committed to a career in science when you arrived?

Ullrich: Well, to be honest, I was not really sure. I just knew [I didn't want] to work in a big company. So that was clear, and that also resulted in my hesitation to join Genentech.

Hughes: Because it was a small company?

Ullrich: No. I had this picture that in a company, somebody's there who tells you what to do. That was not my thing. So, I wanted to be free and do research and follow my curiosity. So that was essentially the picture I had. I thought I would go back to Germany and join some university and do some research there, and maybe do some teaching also. But it was not very defined what my plans were. Then, after

living here for a couple of years, of course, I liked San Francisco very much, and I wanted to stay here. I had then a job offer from Germany in 1978--pretty good job offer--to become a sort of a group leader of an independent research group at the University of Cologne, which then, after thinking for a long time, I declined. And I had a job offer from the European Molecular Biology Laboratory, which is probably the most prestigious institution in this field of research in Europe. That was in Heidelberg and after long struggling with the decision, I declined that one too and decided to go to Genentech.

The whole process how it happened that I really ended up at Genentech was an interesting one because as you probably know, Genentech was founded already in 1976 by Bob Swanson, and he recruited Herb Boyer as co-founder. That [recruitment] was in ’77 after my paper on insulin cDNA [complementary DNA] cloning appeared. So, Bob Swanson was after me and wanted me to become the first scientist, actually, at Genentech.

Hughes: So, it was Swanson who found you rather than Boyer.

Ullrich: Well, Swanson was in constant contact with Herb Boyer. In the context of the insulin project, there were contacts with industry, like with Eli Lilly. They contacted Bill Rutter and Howard Goodman and tried to get an agreement, a contract, with UCSF to get rights to use this insulin clone. At that time, that was rat insulin. As you remember, there was a moratorium on using human material for cloning until the beginning of ’79. So, there were these hot negotiations, and there were at one point also negotiations between Howard Goodman and Herb Boyer and Bob Swanson about him and me joining or having a collaboration with Genentech. And, during that time, Howard Goodman and Herb Boyer, who used to be very good friends and cooperation partners, sort of broke up their relationship, because of Howard Goodman in essence being jealous that Herb Boyer was really the founder [of Genentech] together with Swanson, and he was sort of left out.

Hughes: So it was Genentech that came between them, rather than some scientific dispute?

Ullrich: Yes, it was Genentech. Independent of these negotiations, which then essentially fell apart--too bad because there was also a stock award involved.

Hughes: Which you would have benefited from?

Ullrich: Which I would have benefited from and Howard Goodman even more, but not as much as for Boyer.

Hughes: Was that the bone of contention? That Goodman would not be getting as much stock?

Ullrich: Yes. Independent of all that, Bob Swanson started to pursue me and try to convince me to join Genentech, which did not really exist [physically] at that time. The first meeting I had with him was in Sansome Street in his office [in San Francisco]. I told him that I was not really interested. As I told you before, I did not really want to work for a company, even though I didn't know what Genentech would be like.

Hughes: Were you aware at that point that Genentech had the somatostatin project going on?

Ullrich: Oh, yes. That was going on at UCSF.

Hughes: Were you a friend of Herb Heyneker?

Ullrich: Absolutely. So we were communicating with Herb and Paco Bolivar. There were some funny circumstances—Swanson once picked me up at UCSF and took me to a bar to talk to me again about joining Genentech. That was the famous Chelsea Pub that was the hangout of the postdocs, including Peter Seeburg and John Shine. That was only the Howard Goodman lab; mostly the Herb Boyer people did not go there as far as I remember. So we went to the Chelsea Pub, and they had these game machines at that time—very primitive compared to what's available today. There was one machine that was like a tennis game which was essentially a flat-table screen where one could move bars. A ball bounced off these bars, and you had to catch it and shoot it back and stuff. Swanson challenged me and said, "Okay, we play a game. If I win, you will join; if you win, you still have free choice." And I lost. [laughter]. Nevertheless I said, "No, I will not do it."

Hughes: Do you remember the year?

Ullrich: This was the second part of '77. So the pressure or the recruitment effort continued, and eventually in early '78 I said, "Okay, I'll do it."

Hughes: Swanson was approaching just you? Because of course we know that Seeburg and Shine were also asked to join Genentech.

Ullrich: He was approaching me. I don't know if there was anything going on with Herb Heyneker. I was the first one. I also always said, "Well, if I do it,"—that was then when I finally agreed to do it—"then I would really prefer if John Shine and Peter Seeburg would join too."

Hughes: Why do you suppose Swanson hadn't thought of that himself?

Ullrich: Peter didn't have a very good reputation at that time. He was very unstable. He was into drugs, and he had moved out of his family apartment.

Hughes: Wasn't it enough that he had the growth hormone clone? Wasn't growth hormone on the list of potential products that Swanson and Boyer had?

Ullrich: At that time, the market for growth hormone was very small; it was not a high priority thing.

Hughes: I see. So it was the insulin that was the big deal?

Ullrich: Insulin was what they were after. And there were also negotiations before in the context of the negotiations with Howard Goodman and so on about making this clone available to Genentech. Actually, I just remembered: these negotiations between Swanson, Boyer, and Goodman were going on without Bill Rutter. Bill Rutter heard about this accidentally. "Well, there are no negotiations without me." So he wanted to get in. In the end, these negotiations fell apart because Goodman and Rutter just wanted too much. That is something Genentech could not deliver. Okay, that was a backtrack.

So insulin was their main focus. That's why Howard pursued me mostly. So then I agreed sometime in February, March or so [1978]. Swanson then invited me to come down to South San Francisco. On site, I signed the contract. So I drove down there in my junk yard car, '67 Chevy Malibu--

Hughes: With dreams of better things? [laughter]

Ullrich: Yes, of course. They told me they would pay me forty thousand dollars salary and I thought, "It was outrageous, I have so much money."

Hughes: And what about stock options?

Ullrich: I didn't even ask about them. I had never [before] owned one single share of anything. This was inconceivable to me that shares at some point would be worth something.

Ullrich: I drove down there. Herb Boyer and Bob Swanson were there. The facilities were in the process of being built. There were all these workmen around hammering these beams together. It was sort of a construction site. Boyer was there and Swanson and one guy who was essentially the first real employee of Genentech. I forgot his name. He was sort of a chemical engineer or so. Bob Swanson had this idea: "I want to show to the investors right away that this is going to be a serious company." So he had bought from Eli Lilly a fermenter—big, big thing in which he could grow bacteria to produce insulin. It was very impressive with all these vessels and pipes and valves. This guy was supposed to run this fermenter.

Anyway, I signed the contract. The contract contained an offer of forty thousand dollars salary and 1,250 shares of Genentech stock. I didn't know if that was a

lot or not. I drove back, and on the way I thought, "God, what have I done? I've signed a contract to work at a company." I had no idea what this company was going to do. There was no evidence at that point that something like insulin or something else could be produced in bacteria. The only thing was somatostatin, and that's a twelve amino acid peptide. Only a miniscule quantity of this peptide was detected within the bacteria that were supposed to make it. So, everything was totally uncertain. I started panicking—"No, I can't do that." So as soon as I got back to my room on Frederick Street, I called Swanson and said, "Look, forget it. I take my signature back." [laughter]

Hughes: What did he say?

Ullrich: So, this must have been in early '78. He was disappointed, of course. So he started recruiting [Dennis] Kleid. Kleid brought along Dave Goeddel. Kleid had his lab at Stanford Research Institute, SRI. Dave Goeddel was his postdoc; he brought him along. But I didn't know all that. I didn't know these people. Herb Heyneker was then recruited and joined in '78.

Hughes: It doesn't sound as though you and Herb had been talking back and forth--I've got this offer, you've got this offer, what are you going to do?

Ullrich: No.

Hughes: It was all independently decided?

Ullrich: Yes. I don't think I talked to him about it.

Hughes: I wonder why not. You knew Herb, and you knew he was working on somatostatin for Genentech. It might have been logical for you to say, "What about this group of people?"

Ullrich: You're right.

Hughes: Maybe you were too busy with the insulin.

Ullrich: I was very busy. I still remember very well when Herb Heyneker said once, "Well, if you succeed in cloning human insulin," because attempts to clone human insulin were going on at that time, "then you will get a lot of recognition and so on." But, I don't exactly know why [we didn't talk about the job offers]—or maybe we did.

Cloning Human Insulin

Anyway, that was the next step: clone human insulin. That was not possible in the U.S. [because of the NIH recombinant DNA guidelines]. But this

arrangement with Eli Lilly had been made. Eli Lilly had essentially rights to everything that we did in the insulin project. What Lilly did then was at the beginning of ’78 they decided to do the cloning of human insulin, which was not allowed to be done in the U.S. except in a P4 [physical container 4] facility which only existed in Fort Detrick. [Lilly decided] to do that in France because France had guidelines that allowed the cloning of human material in P3. So the plan was then to build a P3 facility in France, do the cloning there, then it was allowed to bring purified, cloned, plasmid DNA back to the United States. Characterization was supposed to take place in the lab here in [South] San Francisco. Then, possibly, the construction of expression vectors could also be done here and then the cloning again in France. In August, ’78, I started traveling to France back and forth. The facility was near Strasbourg where Eli Lilly had a small factory that produced perfume, Clio, and they had a facility that produced gelatin capsules for pills. So they built this P3 lab. That was approved by the French authorities, and I went there to do the cloning.

Hughes: It seems to me that your work had convinced Lilly that they had to jump into this recombinant DNA game.

Ullrich: Yes, of course.

Hughes: It must of cost a pretty penny to build a P3 lab.

Ullrich: They planned this in very much detail as you will see in a minute and as you probably know already, because they didn’t only pursue this track but they also had to make arrangements with Genentech.

Hughes: Did you know that at the time?

Ullrich: No, I didn’t know. And that was that. I worked and I traveled back and forth. It was exciting. They paid me a consulting fee, and I had good food there in France. Actually this was very close to where my parents lived so I could visit them frequently and my friends from Heidelberg—the region where I come from. So this was an exciting time. I went back and forth in August and September. I think it was October 10 or so or October 7, the director of this facility, a Frenchman, called me into his office and said, “Look, I have to tell you something. Lilly has an arrangement with Genentech to clone chemically synthesized insulin A and B chains.” I knew that Herb Boyer was trying to do that. Boyer had told me once. But I thought it was nonsense because no one has every synthesized such long pieces, chemically synthesized DNA. But they had made them in short pieces, overlapping. So he told me that they had succeeded to do that and to actually express A and B chains in *E. coli* and had succeeded to put them together to some extent and generate active insulin.

Tensions at UCSF

Hughes: How did you feel?

Ullrich: I felt terribly disappointed and cheated somehow. But at the same time, and that's something I didn't say yet: Since the beginning of '77 when the cloning of insulin was completed, these patenting efforts of UCSF were ongoing. They had hired a patent lawyer, Larry [Lorance] Greenlee. Larry was supposed to write a patent, which he did. Then there were these arguments and discussions about who should be inventor. So because growth hormone had been done at that time too, eventually they decided on the basis of reasons I never understood that it would be best to put insulin and growth hormone together in one patent application and have as inventors only the senior investigators, Howard Goodman, Bill Rutter, and John Baxter. We were of course outraged about this but they promised that if ever anything came out of this that we would participate in the proceeds. But we thought it was unfair. In retrospect, it would have been stupid because American patent law says that if the real inventors are not on a patent, then one can invalidate the patent. But we didn't know that. So, anyway, this inventor issue went on and on and was changed. Then they took the patent apart again. Then they said, "Okay, now everybody should be on the patent." It was a mess, which caused a lot of anger against Howard Goodman and Bill Rutter.

On top of that, I had talked during that time with Howard Goodman about staying on at his lab, and he said, "Yes," he wanted me to stay on. I said "But I don't want to be a postdoc anymore." So he offered me a position as assistant research biochemist, which I then became, which was sort of a glorified postdoc. But he insisted that he would be the senior investigator so that I could not publish without him. I was ready to accept this because I wanted to stay in San Francisco, even though I was not happy about it.

Hughes: How common was that system for UCSF?

Ullrich: Very uncommon. I also started to apply for assistant professorships, one in Berkeley, which I did not get. I suspected that Howard was just not supporting me enough. It was a split thing. On one hand, he felt he needed me. On the other hand, he probably was competing. It was clear that we were also not very happy about how the insulin PR part was handled. Howard was really not in the lab; he was on sabbatical during '77 and '76. He suddenly presented himself as the one who was in charge of this [insulin project]. In all honesty, if he had not gone on sabbatical, this project would've never happened because he was completely negative and never encouraging and optimistic that the project would succeed.

Hughes: Did he give you a scientific reason for why he thought it wouldn't succeed?

Ullrich: No, he's just in general a very negative person. He's one of these people who perceive everything as negative that will make it impossible that something is successful. I remember when I showed him one of the first results of the cDNA synthesis effort. He said, "This can't be. This is impossible. This must be some artifact," even though it was beautiful, clear-cut data. So there was this tension.

In October, when I was contacted [by Genentech], calls were going back and forth also with Peter Seeburg. Then Peter told me that Swanson wanted to renew his offer [to me] to [join] Genentech. Peter had in the meantime received an offer also and accepted

[End Tape 3, Side A]
[Begin Tape 3, Side B] ##

Hughes: Swanson had the DNA synthesis technology and it had been shown to be successful. Why did he need the cDNA approach?

Ullrich: Well, they knew that this was not a success that would last or that was really the way to go. Boyer or whoever thought that one would have to do the cDNA cloning. I had a good reputation that I could make things work. And then of course it was that Peter Seeburg wanted me to join, and I guess also Herb Heyneker. We were the ones who had the most experience in this [cDNA cloning], probably in the world. Also, maybe a little insecurity—get a strong team together. Then if things don't work out, well, we are a team and we can do something else together--or whatever; I don't know.

So I decided to do it. But I wanted to do it differently than Peter because Peter had left [UCSF] essentially in anger and with strong disagreement with Howard Goodman. Howard had essentially kicked him out of the lab. He didn't allow him to enter the lab anymore. He locked up his freezer. He put a chain around the freezer where Peter had his clones. So I wanted to avoid this kind of thing, and I said, "Look Howard, I would like to continue on the insulin project, and can we continue to collaborate?" And he agreed and said, "Okay, yes, but I have to become a consultant for Genentech." Again, he wanted to have as many shares as Herb Boyer. And of course this was impossible.

On the last day of '78, I had packed up all my things, including a box with reagents and clones and so on. Peter Seeburg, who had been banned from the lab, knew that I was leaving that evening, New Year's Eve '78. So he had asked me if he could come with me at night and get his own clones too. So not very sympathetic to Howard Goodman at that time, I said, "Okay." We both, in the middle of the night, essentially before midnight, went into the lab, and we get Peter's stuff and my stuff. We left and we were scared of encountering the campus police.

Hughes: Nobody else was around?

Ullrich: No. We got out without being questioned.

Hughes: But how did Peter get his stuff out of the locked freezer?

Ullrich: Well, it was not locked anymore because Peter had left three months before. So, that was this famous midnight raid. I told this story yesterday at UCSF as the introduction to my talk. If [the raid] had not happened, it would have made it more difficult for Genentech to get this growth hormone project done, would have never led to a trial, UCSF would have never gotten this settlement, the [Genentech building on the UCSF Mission Bay campus] would not be there, and Peter Seeburg would not be rich. And the most ironic thing about the whole thing is that Howard Goodman tried everything to prevent Peter from doing that, [but] Peter did it anyway and I helped him, [and Peter] became rich because of that. And the same thing with John Baxter and Joe Martial and all the other guys. And I didn't get a penny out of this. Not even a tip because I was the driver.

Does that make you bitter?Hughes:

Ullrich: No, it's only money.

Hughes: It's only money?

Ullrich: Honestly, I never had any hard feelings about that. But it's still interesting that they didn't even say thank you or something. And it's interesting also that I was never asked to testify in the growth hormone case.

Hughes: I would have thought you would have been a prime witness.

Ullrich: Yes, I would have thought so, too.

Hughes: Well, why do you think that is?

Ullrich: I don't know. Lawyers decide.

III. THE HUMAN INSULIN PROJECT AT GENENTECH

Hughes: You and Peter arrived at Genentech about the same time, am I right?

Ullrich: Well, Peter was there three months before me. Or two months. He started in November [1978], I think.

Hughes: What had been the discussion on specifically what you should do?

Ullrich: Well, that's an important point. I of course had pretty clear plans of what I wanted to do. The exciting thing at that time was that the world was open, and there were so many things that one could do scientifically.

Hughes: You mean specifically with recombinant DNA?

Ullrich: That's right—this technique and our experience. So, it was really like, "Okay guys, let's do it." But, on the other hand, there were not that many obvious projects that would result in a product for Genentech. It was clearly insulin. So that was obviously my first personal interest, and that was in the interest of Genentech, of Bob Swanson—to clone human insulin again. I had left the human insulin cloning project for Lilly unfinished at UCSF, even though I had clones isolated that were characterized and were human insulin. But it was not a completed project. So I went to Genentech and was supposed to do the same thing again.

Hughes: Now, I'm missing something. Genentech had succeeded, as you said, in cloning insulin by piecing things together, using the synthetic DNA route. Why not just continue with that approach?

Ullrich: Well, because I was convinced, and others supported that, that it would be easier to do upscaling of the production of insulin by going the cDNA route, by doing pre-proinsulin, because then you don't have the two chains, A and B, but the two chains connected by the C peptide. And the proinsulin was too large at that time to really— I could have probably done it but it was not that simple to do with the chemical synthesis approach so therefore I wanted to clone human proinsulin. They also had agreed with Eli Lilly that that would be the way to go. So that was clear.

Choosing Research Projects and Publication Policy

But I had my own ideas, what else I wanted to do, even though these other projects [of mine] had no obvious commercial potential.

Hughes: You were already thinking of growth factors?

Ullrich: Growth factors because there was this gene family, and the peptide sequence was known of IGF-1 and IGF-2, insulin-like growth factors. It seemed scientifically attractive to clone related genes and see how one could deduce the rate evolution had taken place and generated these factors.

Hughes: Now, had this type of research been a discussion point with Swanson in the hiring process?

Ullrich: Oh, it just opened [as an opportunity], so I insisted that I do my own thing and that I decide myself what I would want to do.

Hughes: Even though there was no obvious product?

Ullrich: Yes.

Hughes: And he agreed?

Ullrich: Well, grudgingly. He had to accept a few other things at that time. There was this group of self-confident and capable young scientists that included Dennis Kleid, Herb Heyneker, Dave Goeddel, Peter, me, and a guy named Giuseppe Miozzari. We had senior scientist meetings. I remember we were so into doing the work that none of us wanted to be the research director. So we decided Giuseppe Miozzari was the one with the least experience, and he was not known to be good at the bench, so he should be the director. So that's what happened.

I took this initiative: Look, what will happen if all of this [research at Genentech] is going to be a bust? It will not work out? We will have to start looking for jobs in academia again. And in order to be able to do that, we have to publish.

Hughes: So the publication policy wasn't in place when you arrived?

Ullrich: No. I initiated that. We called Swanson and talked it up, "You have to allow us to publish what we are doing here." "Oh, no." Then I think Herb Boyer just convinced him that this was a good thing.

Hughes: But the idea came from you?

Ullrich: Yes.

Hughes: I haven't heard that before. People talk about it coming from Herb.

Ullrich: No, no, no, Herb only approved it. I remember very well this meeting where we discussed this, and there were pros and cons, and Swanson was against it. So, this was the beginning of essentially a new culture of doing science. A small company that nevertheless was very open and liberal about [publication]— [cell phone rings] A piece of [policy was] installed that was good for all of us and also for Genentech.

Hughes: It's interesting that it was premised on a negative.

Ullrich: Of course.

Hughes: The right to publish became very important, did it not, in attracting top-notch scientists?

Ullrich: Yes.

Hughes: It wasn't quite like publishing in academia. There was a certain amount of review before a manuscript went out?

Ullrich: Formally, yes, but in reality, no. It was essentially up to us to tell the patent lawyer. Tom [Thomas D.] Kiley was the key person then. I don't know when he started.

Hughes: 1980, in house.

Ullrich: So before that we didn't have a lawyer in house.

Science for Science's Sake

Hughes: Do I deduce from that fact that the intellectual property aspect of a company such as Genentech was at first downplayed compared to the science?

Ullrich: Well, one cannot say that in such a general way. For me, commercial application was not really number one in my mind. I was driven by the interest in science. This attitude was very very different in the group from person to person. Clearly Dave Goeddel excelled at that time as the one who was really determined to do whatever Swanson told him and whatever seemed to be at the moment the best for Genentech. It's ironic looking back, me being naïve saying, "I just want to do the science." I generally did more applied projects than anybody else there. [laughs] Most of my projects that I initiated myself developed a commercial potential.

Dave Goeddel was a maniac at that time. He had just gotten married. His wife was pregnant, and he spent all his time in the lab day and night working on interferon. One project that Swanson wanted me to work on was the interferon. But Dave Goeddel sort of took that project over because it seemed to be the most attractive one at that time that could be most important for the company as well and generate the most fame. And tragically, even though he worked incredibly hard, we were beaten by the Biogen people, Charles Weissmann.

Hughes: But it didn't turn out to be much of a product immediately, did it?

Ullrich: Not immediately. Of course, Genentech pursued it [into] clinical trials and it failed. That was a big disappointment.

Hughes: How do you explain those differences in motivation?

Ullrich: Oh, I would have to tell you a lot more about me.

Hughes: Well, that's all right! That's what we're doing. [laughter]

Ullrich: Better not. I don't know. Maybe it was a feeling that I would fail if I would get into these super competitive projects, even though insulin was super competitive, and everything else that I ever did before and afterwards was always competitive. I'm always driven till today more by my gut feeling than by intellect. I'm not somebody who plans and calculates and all that. Swanson recognized that at one point. He said, "Well, yes, he has a truffle nose. He knows without knowing why where the good things are."

Hughes: The truffle nose, that's wonderful.

Ullrich: So, that's my reputation. I had so many ideas that I did not really have a chance to pursue, which then others [pursued]. That's my fate--that I have good ideas too early.

Hughes: It seems to me you were driven by the science, and if there happened to be a product so much the better, but that wasn't particularly your motivation.

Ullrich: That's right.

Cashing in Genentech Shares

Hughes: That in a very practical way could be self-defeating because the company could fail.

Ullrich: Absolutely, definitely, because I didn't get these additional shares. I didn't tell you that. When I accepted finally the job offer, they showed me a contract that said I get, I think, four thousand shares. So I thought wonderful, good that I waited for a little while till they increased the number of shares, even though I had absolutely no confidence that these shares would ever be worth anything

Hughes: And you hadn't asked for more?

Ullrich: I hadn't asked for more shares. But then I found out, in the meantime, they had done a share split of one to ten, so I ended up getting significantly fewer shares.

Nevertheless, I still didn't believe they would be worth anything--ever. But then, at one point, Swanson told us those people who wanted to sell some shares (that was before we were public), could do so for ten dollars a share. So I was surprised and pleased. I decided to sell some shares, I think eight hundred shares of my four thousand, because I wanted to buy a new car. I had this car that I had bought for $250 which was breaking down all the time. So I decided I would buy a used VW Rabbit. So I sold I think eight hundred shares for eight thousand dollars. And then there's this joke that Dave Goeddel likes to tell everybody that after we had gone public, the stock price went up and up and up. At some point, these eight hundred shares were worth more than one million dollars, and I bought a used Rabbit for that, a million-dollar Rabbit. Oh god! [laughter] [interruption]

Genentech Culture

Hughes: Say something please about how you found the work culture, the spirit, at Genentech as compared to what you had experienced at UCSF.

Ullrich: Well, I didn't have much experience. It was just a very exciting time. You could feel the excitement. People worked day and night, and I worked day and night. It was also, of course, very challenging. Peter was in terrible shape. He was practically unable to function, to work. We shared an office, and we were in the same lab.

Hughes: Did you feel some responsibility?

Ullrich: Oh yes, absolutely. Well, it all worked out fine, but this was a hard time for Peter. During that time, you know, we were all paving the way for our future.

Hughes: And he wasn't doing much scientific work?

Ullrich: He didn't do much. He came in late, and it was obvious not only to me but to everybody else. This lasted into 1980. Swanson and Kiley were incredibly good to him. They were supporting him and offering all kinds of things--professional help. So, this was very good that they didn't just say, "You don't perform—out."

Hughes: When you look at the setup at UCSF or any academic laboratory, it's a hierarchy to a degree. I mean, there's the lab chief and then there's the rest of you. I get the impression that it was not that way at Genentech in those early days.

Ullrich: Oh yes, absolutely. We were a very flat organization. Well, I have to say that I was probably not a very good, cooperative employee at that time.

Hughes: Meaning what?

Ullrich: Well, because I just wanted to do what I wanted to do. So Swanson of course preferred then to support and interact with people who were less troublesome, like Dave Goeddel and Dennis Kleid. But Swanson also never said [to me], "Okay, you can't do that." Over time, I gained their respect, and they understood that what I was doing was good and led to publications in good journals and increased the reputation of Genentech as a science factory.

Hughes: Was there a point when you began to think that the company would be a success?

Ullrich: Oh yes. Definitely at that time Dave Goeddel was the one who did the projects that looked like they could be very good commercial projects. They did not really work out until tPA. So interestingly, the first two projects that led to commercial applications were mine and Peter's. So insulin and growth hormone.

More on the Human Insulin Project

Once I was to give a talk in Germany at the Diabetes Research Institute in Munich. And I talked there with a doctor who worked with patients about my efforts to clone human insulin. This doctor told me he had an operation upcoming on a patient that had a tumor of the pancreas of the Islets of Langerhans, a so-called insulinoma. These patients had too much insulin so this tumor had to be removed. So I said, "Well, this is exactly what I'm looking for. Could I get this, this tumor?" And he agreed. This tumor was from a farmer's wife out of the Alps, and this tumor generated the RNA that led to the clone of a complete human cDNA, which we published. Dennis put it into an expression vector, and this is the one until today, I believe, that produces human insulin.

Hughes: The Gilbert group had an insulinoma.

Ullrich: They had this Chick insulinoma that was a rat insulinoma. They had this insulinoma that this person named [William] Chick had found and propagated. They could generate essentially large amounts of insulin so they had an advantage over us. But that was rat.

Hughes: What did you do for the insulin project at Genentech? You were meeting Eli Lilly deadlines, were you not? There were benchmarks?

Ullrich: Yes.

Hughes: Were they important to you?

Ullrich: Not that much, I have to admit. Therefore, I had no objection that Dennis Kleid was doing the insertion into the expression vectors. But while I was cloning--

Hughes: So, you were the cloner?

Ullrich: I was the cloner.

So, while I was cloning the cDNA, I was also screening for these insulin-like growth factors using, actually, the rat insulin probe from UCSF.

Growth Factor Research

Hughes: Maybe it's the time to bring in the growth factor story.

Ullrich: Well, it was not as easy as I had thought. But eventually I succeeded.

[End Tape 3, Side B]
[Begin Tape 4, Side A] ##

Hughes: Why did you think it was going to be easy?

Ullrich: Well, I thought the sequence homology to insulin was good enough. But our technological know-how at that time was not good enough, so I eventually resorted to oligonucleotides, which we had available. We had this DNA synthesis group--

Hughes: Roberto Crea?

Ullrich: Yes. It took much longer than I had hoped for. I also had cloned NGF, nerve growth factor, cDNA. Eventually, these projects were successful and published in good journals, but always in competition with UCSF. Bill Rutter and Graeme Bell.pursued essentially the same direction that I did. So they were always in competition. Sometimes they won, sometimes I won.

Hughes: Were you in contact with them in any way?

Ullrich: No. This was a tense time. We were really considered to be the outcasts or the deserters.

Commercialization of Biology

Hughes: So the Genentech group was very self-contained?

Ullrich: Yes. Chris[tine] Guthrie and Keith Yamamoto were young critics at UCSF. And, of course Bill Rutter especially had a very competitive sense. Graeme Bell also.

Hughes: But in a different way from the critics, right? Rutter was competing scientifically. Did he ever express any reservations about academics going into the corporate world?

Ullrich: No, not him. Only the other guys who were set on the moral route.

Hughes: Did any of their arguments hold water as far as you were concerned?

Ullrich: No.

Hughes: How did you explain to yourself the conflict over commercialization?

Ullrich: I thought that they were just jealous. Later on they played the same game and they all joined. Later on they had to see that we not only were sort of after the dollar but we were also publishing good papers.

Hughes: You could certainly stand on your good science. One of the issues, critics claimed, was that biology was going to be corrupted by being turned to commercial uses.

Ullrich: Yes. We didn't worry much about that, and I certainly didn't.

NIH Guidelines for Recombinant DNA Research

Hughes: Another issue is the recombinant DNA controversy and of course the NIH guidelines. How much were they in your consciousness at Genentech?

Ullrich: At Genentech, the situation was different because the guidelines applied only to academic research, so commercial enterprises were not obligated to follow those guidelines. Nevertheless, Genentech voluntarily complied.

Hughes: And why do you think it did? What was Genentech's motive?

Ullrich: Well, it was all sort of a political thing. They wanted to show that we were not irresponsible monsters. It was good for Genentech.

Hughes: Are you then saying that the guidelines didn't have much impact on what you were doing in science?

Ullrich: Yes, I would say, no impact at all, especially after the ban on cloning human DNA was lifted.

Hughes: Do you remember when it was?

Ullrich: In January of '79.

Hughes: Why did people become comfortable with the idea of cloning human DNA?

Ullrich: I guess because there were lots of ongoing activities, and there was no accident rate, nothing had happened. None of the irrational fears had come true or were justified or realized, so the committee just decided that it was okay.

Hughes: And possibly because you at Genentech were showing that this technology had commercial implications.

Ullrich: Well, not only commercial--medical implications.

Hughes: Well, commercial leading to medical.

Ullrich: Yes, yes.

Corporate Organization and Culture in Biotech

Hughes: Genentech must have had a sizable role in making that very point. What other company would have been making it? Biogen?

Ullrich: Biogen was established in Switzerland.

Hughes: I think Biogen was established in '79, and it was very early 1980 when they cloned the first interferon.

Ullrich: Yes, well that was done in Charles Weissmann's laboratory. Biogen had been founded on this concept: Get a few big shots together and commission the labs to do a project, which did not really work out too well because too many big shots are counterproductive. [laughter] And, this was proven. Nevertheless, this one project, interferon, really saved Biogen,.

Hughes: Genentech, I suspect not by deliberate calculation, went the opposite route. They had a lot of young punks.

Ullrich: Yes, and that was good.

Hughes: Do you think that was thought out?

Ullrich: Well, I'm sure Swanson wanted to make sure that all the intellectual property was generated in house and stayed in house. He was a penny pincher. He hated having to pay people for something. Therefore, the whole relationship with Riggs and Itakura was also a little bit influenced by that.

Hughes: What do you mean by that?

Ullrich: Isn't there some kind of feud ongoing?

Hughes: Yes, Genentech has appealed the decision in its case with the City of Hope.

Ullrich: Clearly, Swanson wanted everything done in house. He even once called me--that was before I joined Genentech--while I was trying to clone the human insulin in France. He said, "Well, why don't you stop working on this because you will be hurting Genentech that way." He was very possessive. The first CEO of Biogen was not really so committed to the company and to winning. I met him only once but I heard much about him. He was then at one point removed from his post. So they thought probably it was cheaper to pay grants to different laboratories and have projects done in the laboratories. But this was definitely not the right way to do it

Very important, and I learned this from the early Genentech times and later on over and over, when you start a company, no matter if it's biotech or some other [kind of] company, a very important driving force is the identification of the employees with the goals of the company. Even though I was not the prime example of such an employee, I was just pulled in. We were very excited about Genentech and this feeling of belonging--very important. Rationally or not, I was just pulled into this stream of conviction that we were on the right way and that we were doing something important and exciting.

Did all the early scientists feel that way? Were they 100% committed?Hughes:

Ullrich: Yes.

Hughes: To what degree was Swanson encouraging this commitment? Or was it the science?

Ullrich: He was doing that just by being one of the boys. But I have to say also there was one reason why I was not more actively involved in everyday activities. There was clearly a difference of cultures, European versus American. Many of these expressions of team spirit which people acquire here, especially males in college and high school, like shouting, "Do it guys! Beat them!"--it was very foreign to

us [Europeans]. [Yet] the one who was the most adjusted to this kind of behavior was Herb Heyneker. He behaved more [like the] Americans. But Peter and I were more on the sidelines.

Hughes: And Giuseppe Miozzari?

Ullrich: He tried, he tried. Of course, Swanson appreciated that because he was familiar with that.

Hughes: The gung-ho stuff?

Ullrich: "Let's do it guys!" And the DNA battle cry, and that kind of stuff.

Hughes: Where was Roberto Crea in all of this?

Ullrich: Well, he was half and half, I would say. He had a sense of what was good for him and his career, while I didn't.

More on Growth Factors

Hughes: Well, I don't think we've done justice to the growth factors. Do you want to say more before I get to the question of Herceptin?

Ullrich: Well, actually the growth factors led to Herceptin.

Hughes: Exactly.

Ullrich: At this time, '82, '83, it was still not clear whether NGF or EGF [epidermal growth factor] or something [else] would ever have commercial potential. Nevertheless, I started and also as a demonstration of my determination to do something that would be good for Genentech. At that time, I was very much looking for uses of these growth factors which, given the state of the science--physiology and biology--of these growth factors, was not easy. So there was a lot of speculation.

Hughes: It was a hot field, was it not?

Ullrich: Yes. Well, I started it, together of course with Bill Rutter as competitor. So we made all this possible. But I should also explain that while I was at UCSF I collaborated with Mike Bishop's lab and Harold Varmus's lab. We were on this oncogene business that kept on going. But there was absolutely no evidence that there was a connection between oncogenes and human cancer; there were only animal models. So one could have said, "Oh, it's an accident of nature that these

animal retroviruses would cause cancer," which is actually true today. There is no human tumor virus known.

Hughes: Isn't there HTLV?

Ullrich: But they don't carry an oncogene. They can cause cancer by weakening the immune system. But they are not oncogene-based retroviruses. I lived in a house where two women lived who worked in Bishop's lab. I was constantly exposed to these discussions about oncogenes . But I had not at that time the intention or the plan really to do something.

This afternoon I'll have a discussion about that with Dennis Kleid because Chiron is suing Genentech about Herceptin and stuff. They claim that they discovered it earlier.

Hughes: What is the basis of their claim?

Ullrich: It's ridiculous, it's crazy, but lawyers make everything possible. Once Chiron was founded, one of their projects was to take human tumor cells, breast cancer cells, and inject mice with these cells and generate as many monoclonal antibodies as possible against the whole cell. They actually made more than, I think, fifty thousand monoclonals--a huge effort--without knowing what they were looking for. One of the ideas that was around and that had been pursued rather unsuccessfully was tumor markers. Tumor markers are molecules on the surface of tumor cells that are unique to the tumor and could be used as targets for antibody-based destruction strategies. So that's what they were pursuing. They had these huge collections of monoclonal antibodies, and they classified them. It was actually an amazing effort, I have to admit. They made toxic conjugates, of course not with all fifty thousand. That was their screening concept. They made conjugates with ricin, and then put them on tumor cells. When the tumor cells died, they saved these monoclonals. But they still didn't know what the antigen was, so it was sort of a blind approach.

Now, years and years later after we had done all the Herceptin and the HER2 cloning, etc., etc., they checked some of these clones and found that they had some clones against HER2. But since they had isolated these already in '82, they came back and said, "Okay, we discovered antibodies and therefore the antigens. Therefore we were first." Chiron wants a significant portion of the income from Herceptin, from Genentech.

Hughes: My understanding is that you made a correlation between HER 2 and breast cancer while you were at Genentech.

Ullrich: Yes.

Hughes: What did Genentech do with that information?

Ullrich: Nothing. Let me tell you from the beginning. The story evolved directly from the growth factors. One project was to clone EGF cDNA, epidermal growth factor. Epidermal growth factor is a peptide of fifty amino acids, so very short. Sequence was known. We started to screen with oligonucleotides from that sequence, and we succeeded. It turned out, the precursor EGF was part of the long precursor which contained twenty-five EGF-like sequences. The whole precursor, I think, was 1250 amino acids. So huge. It had—and that was also a first--a sequence that was clearly a transmembrane domain.

Hughes: And that was new?

Ullrich: Yes, but again competing with Rutter, and I think we published at about the same time. So, that was very intriguing. I wrote a *"News and Views"* article [in *Science*] at that time saying, is the precursor a receptor? Because it looked like what we thought a receptor would look like. But at that time there was no receptor sequence known.

Hughes: And you thought it looked like a receptor mainly because it was transmembrane?

Ullrich: Because it had a transmembrane sequence. The connection to the next project came through Mike Waterfield. Mike Waterfield was a scientist at the ICRF, Imperial Cancer Research Fund in London. And he was a consultant to Baxter [International, Inc.] who had at that time some sort of project negotiation on-going with Genentech, and therefore Mike Waterfield was visiting. I met him and I showed him the sequence. He actually pointed out to me that there was a transmembrane domain. So we got along very well right away. Therefore, a short while later--that was in 1983--he called me and asked me whether I was interested in collaborating with him on the cloning of a receptor named the EGF receptor. He had started a collaboration with Joseph Schlessinger. Mike Waterfield's was at that time one of the best labs to do protein synthesis. They wanted me to be the cloner, and we were probably at that time the best cloning group in the world. So, I agreed, and that was an idea towards the end of '83.

I got a phone call and Mike Waterfield said, "Look, something really exciting has happened. We've obtained the first peptide sequence--a short peptide like a hexamer of the EGF receptor." A student in the lab, Julian Downward, had used these sequences to search in already known protein sequences, which were not many. A significant number of the known sequences were oncogene sequences. So there was sarc and shortly before the sequence of an oncogene called erbB, had been published. And the student, Julian Downward, found that these peptides matched sequences in this oncogene. So this was super exciting. [Waterfield] invited me to come to London. This was shortly before Christmas in '83. I met [Orwell], I met for the first time Joseph Schlessinger, and we discussed how we should proceed. So a paper was written briefly, just written on the basis of these short peptides, and was published in *Cell*. And we had some

clones on the basis of these peptides already obtained, and so things proceeded very quickly. We got the complete sequence of the EGF receptor, and it was clear that the EGF receptor was the proto-oncogene version of the oncogene erbB. So this receptor was the first connection between cancer and a growth-regulating protein. That was published in April or so of '84. At that time the quickest review and acceptance time was like one month. *Nature* accepted this paper and published it within one month.

Hughes: This was a paper rather than a letter?

Ullrich: It was a full article. So, that was exciting. It was one door opening to understanding how cancer can develop by mutating genes that are regulating the growth of cells. But at that time we didn't know that there was more than controlling growth but also other aspects of cell characteristics. We were still looking for relevance of oncogenes in human cancer. So, here we had EGF receptor and this truncated and mutated oncogene. I wanted to find out whether in human tumors this kind of oncogene could be generated by maybe gene rearrangements. So we did Southern blots on tumor cells, but didn't find anything. But we found that the gene of the EGF receptor can be amplified. And then tumor cell lines, cervix carcinoma cell line, April 31--the gene encoding the EGF receptor was present in about 25 copies rather than one copy. So, gene amplification. But there was no evidence that this was significant for many tumors or tumor cell lines, and there was still no evidence there are oncogenes in human cancer. But then what happened in the course of this project was we found--actually I was doing the project myself, screening cDNA libraries. So I pulled out clones that did not encode the EGF receptor but some other sequence, some other gene that was very closely related. We had at that time established a sequencing group. That was one of the very useful infrastructure installments we had [at Genentech].

[End Tape 4, Side A]
[Begin Tape 4, Side B] ##

Ullrich: Peter came to me once and said, "Look, something interesting I found in our collection of sequences, sequences that are not EGF receptors but are very similar." These sequences had been generated by sequencing clones that Art Levinson's lab had generated. He had, without me at least knowing, screened a genomic library, I think, human, with a probe from erbB, an oncogene probe. And they had pulled out clones, and they were sequenced. But they did not pursue this actively any further. I actually don't know why. Then we continued to look for more clones because these were only fragments of this EGF-related gene. We then obtained the complete sequence of this related receptor. I of course was aware this could lead to tensions. I talked to Art Levinson and told him that he would be part of the paper, co-author of the paper, and we discussed how we should call this gene. So together with him, we came up with this name, HER2.

Hughes: And he was fine with that arrangement?

Ullrich: With him, you never know. He's an extremely political person, in contrast to me. [laughter] So that was the situation. He must have had some bad feelings that I sort of stumbled into this exciting project. I did this EGF receptor project and HER2 without the authorization from Genentech. There was no obvious use for this. They said, "Do you want to sell receptors? What is this?"

Tom Kiley called me, must have been beginning of '84. I went to his office and I knocked and there was Tom Kiley, not looking at me but with his back to me, looking at the wall. He said, "You did it again!" [laughter] He was very much into theatric behavior. He meant, you did something you were not supposed to do even though it's exciting. But it was not authorized.

Hughes: But surely Genentech was going to get kudos for having a scientist who kept writing top papers in a hot field. Wasn't that appreciated?

Ullrich: Oh sure, sure. But not openly. I never got any rewards for that. Nevertheless, Kiley respected me, and he appreciated us doing something good even though he didn't understand what this would be good for.

Hughes: So, what happened in that particular encounter?

Ullrich: Well, he actually said that the company was realizing I was doing great science and so on. He felt I should get recognition, a share award, which I never did get. It was just sort of a joke.

That year something else happened, and I don't know exactly when. It must have been sometime in April, just after EGF receptor was published. We went to a Keystone meeting that was one of the first Keystone meetings. And I gave a talk. Maybe it was in '85 already. This [meeting] was on oncogenes. The last talk was an unscheduled talk by a young guy called Dennis Slamon. And, he showed some pictures of Southern blots with oncogene probes. He was at UCLA, and he collaborated with a more senior person called Martin Kline. This was not very exciting, but it taught me that this guy apparently had access to primary tumors, to real patient tissue. That I was intending to find because I wanted to know whether the EGF receptor or any of the others--I had growth factor genes as well as EGF receptors and this unknown thing, HER2--there was anything in real human cancer that could indicate that there was some gene rearrangement that gave rise to an oncogene-like thing like erbB. I left this meeting early, actually right after Dennis's talk. Dennis was on the same bus, and I didn't talk to him on the bus. But then when we both got out at the airport in Denver, and we went into the airport and checked in, I approached him. I started to tell him about what I was interested in and asked him if he was interested to collaborate. And we sat in this bar in the airport, and we discussed the potential collaboration. So, I started the whole thing. I told him what we had,

that we had about seven probes, and I wanted to check primary tumors and see if there were any abnormalities. I didn't tell Genentech that I was planning to collaborate, and they never really controlled that, so I was able to collaborate with anybody I wanted--at least I did. [laughter]

So then I put these probes together. We made the probes out of the DNA fragments, and I labeled them one through seven and sent them to Dennis. And then I heard for quite a long time nothing from him. Then one day, it must have been already in '86, I got a phone call from him. "Look, yes, first results. It looks possibly interesting." But we still didn't know what was what so I went back to L.A.. and visited him in the lab, and we looked at the data. They [the probes] were numbered. He had done Southern blots. There was one set of blots on breast cancer tumors that looked like there was no gene rearrangement but gene amplification--just what we had seen in these April 31 cells with the EGF receptor probe. And then I told him which gene it was; it was HER2. So this was the beginning of an exciting story.

In my lab, we first checked whether one could transform cells with HER2. It was demonstrated that one could transform, make cancer cells out of normal cells in [?] cells, and we started making monoclonal antibodies. I had one post-doc working on this project. This was also an interesting thing in retrospect. This was a guy named Bob Hudziak. He had started his postdoc at Genentech in Art Levinson's lab, and Art Levinson did not get along with him, or he thought Bob Hudziak was crazy. I knew Bob Hudziak was crazy, but he was extremely smart at the same time, but he was socially, totally strange. So I put him on the HER2 project. At that time it also became clear that this was developing into an exciting and important project. One other person at Genentech who didn't have a project was Mike Shepard, who jumped on the train and helped on this project. We made monoclonals and tested these monoclonals also for their ability to enable the growth of tumor cells. Six or seven or nine were able to do that, did that also in an animal model.

I at that time continued to push. Now it was not about producing receptor and selling receptor for nothing, but about an antibody that could inhibit the growth of tumor cells which could be a therapeutic agent. Swanson was-- I don't know how many meetings I had about this where I pushed, "You should do [develop] this." They were not interested. And that's when I had an offer to go back to Germany, become a Max Planck director. I then accepted that. I had essentially no support for this project even though it seemed so clear it was promising.

Hughes: What were Swanson's reasons?

Ullrich: Well, there were several, I think. At that time, antibody drugs, even though that was an established concept, had not been shown to be successful and be working. There was a company that had been founded on that basis, Centocor. And they had failed. At that time, they had one antibody, but they didn't do

target-specific things. They had screened antibodies in some kind of test. They had developed an antibody that was supposed to work in sepsis. And the antibody failed in the clinic. One of the first biotech crises was caused by this failure. So stock prices went down.

Swanson was suspicious. He didn't like antibody and he didn't like cancer because Genentech had tried to develop anti-cancer drugs--alpha interferon, tumor necrosis factor, gamma interferon. All of them had failed in the clinic. So, he had this anti-cancer prejudice that this was not a good indication. I really didn't understand why they were against it. So, I left. And at that time already, Art Levinson was positioning himself for a career in Genentech. Genentech had grown large, seventeen hundred employees in 1988. And, it was, it became more and more difficult to get a decision that the project was designated as a development project. Too many people were involved in decision making. It became a big company.

Art Levinson participated in these discussions to some extent, but it was mostly Dave Goeddel, me, a couple of other people. Peter Seeburg had left already. He was back in Germany. We wanted Genentech to establish a separate research facility that was outside of the company. Roberto Crea's company had moved to the East Coast, and there was space available. So, we wanted to add a sort of a spin-out, not out of Genentech, but out of the buildings, go back to exploratory research.

Hughes: To get out of the corporate structure?

Ullrich: That's right. At some offsite meeting where we presented this idea, suddenly Art Levinson talked exactly the opposite. He was sort of abandoning us, "us" meaning especially Dave Goeddel, who was at that time also not very happy with how things were going at Genentech. This idea of setting up a separate facility was not accepted.

Hughes: Why would Levinson have been against that?

Ullrich: Well, he played this real opportunistic game, very clever, I have to say. So I decided to leave. But they retained me as a consultant, and so I visited regularly Genentech. I continued to sort of support the HER2 project, which Mike Shepard was essentially taking over at that time. So, there were still activities going on even though they had decided not to develop it as a product. Then Mike Shepard left suddenly, in 1990 or so, and I don't know how this decision came about. Then [Genentech] changed their mind. They decided to make a development project [of HER2], and they started humanizing the antibody. In 1992 the clinical trials began. They were conducted primarily by Dennis Slamon, but he was not involved in the antibody and all these aspects of the HER2 project. As an M.D., he led the clinical trial efforts that eventually led to an approval by the FDA.

Hughes: Did you have to drop out of this research when you left Genentech?

Ullrich: Well, I didn't have the ability to start clinical trials myself and I couldn't have done that.

Sugen

Hughes: Did you turn right around and form Sugen?

Ullrich: The first idea to do that came about in 1990, and then it was formed in 1991. I was still consulting for Genentech, and I went to Kirk Raab at that time and told him about this intention to start a company. I said, I would be very happy if we could collaborate with Genentech because until then they had declared they were not interested in receptors and target-driven drug development and so on. What happened was they sent me an official letter signed by a lawyer telling me that I should realize that everything that I am doing since I left Genentech belongs to Genentech. That was interesting. The other thing was, they had decided to develop HER2. The third was, they decided to pursue exactly the projects that I had started--receptor tyrosine kinases and so on. So they turned around and that without any doubt happened because of Art Levinson. He decided to go after this now. Well, I canceled my consultancy with Genentech. After meeting with a representative of Max Planck Society and myself, they decided not to sue me as they had threatened.

What would they have sued you about?Hughes:

Ullrich: Well, they said in the employment contract, it says that for the rest of my life, everything that I do belongs to Genentech. I don't know how they derived that. I never read any sentence that could have implied that. They were just playing games. It was really odd. I found out yesterday, they did the same thing with another Genentech employee, Rick Dewick. He left, and he went to UCSF to be a professor there. So they threatened him also. They always had a sort of preference for tough [legal] moves; they had lots of lawyers at Genentech always, and they had always something. They like to sue other people and companies.

This is not the end of the HER2 story. Clearly, because of all these claims and trials, Dennis Slamon had attracted a lot of attention. Everybody forgot or was not interested in what the real origins of this project were, including himself. There were interviews and articles and newspaper articles which described the story but completely wrong.

Actual and Potential Awards for Receptor Research

The culmination of the whole thing happened last weekend when I came from Saudi Arabia where I had received a prize [King Faisal International Prize in the Field of Breast Cancer] for the HER2 /Herceptin story. The Max Planck Society had nominated me, and I had told them if they would ever nominate me for some prize, because they had done that before, they should always say that Dennis Slamon was a critical partner in this, and without him, this would have never succeeded and so on. Okay, they gave this prize, nevertheless, only to me, recognizing that I initiated the whole thing and the history with the EGF receptor before, which led the way. So I came back, and last Sunday, I went to the office, and I logged into my email. There was one email from the AACR press release, American Association of Cancer Research, announcing that Dennis Slamon had received a prize, the so-called Landon Prize [for cancer research]. And, so I went on the AACR site that was connected to this prize, and there was this press release describing Dennis Salmon's achievements. Of course, the story was told completely different than what I have told you, told like: After identifying the HER2 gene, Dennis Slamon joined up with the Genentech team--my name was mentioned once--to develop antibodies against HER2. He had conceived this project [according to this press release]. This is science. This is history.

In December, I had meant Dennis Slamon who is still on the Sugen advisory board, and I am on it, too. I had confronted him. I said, "Look Dennis, let's stop this antagonism. I don't want this. We should both get credit for this work, but you have to play along." The reason I was getting concerned was that after the approval of another drug, called Gleevec, which is a small-molecule inhibitor of the tyrosine kinase that is involved in leukemia, in CML [chronic myelogenous leukemia]. A big team from a company named Novartis developed this drug, which is for a patient population of only about 2,500 people every year in the world. [The team] had received a lot of prizes, so I thought, "Well, it would be terrible if they would get another credit for having developed the first target-specific drug. Herceptin is the first such drug. The PR around Herceptin was not promoted by Genentech, at least they did not involve Dennis or me. And of course, the medical community really focused more on Dennis. So I said, "Let's be a better team and promote us as a team." And he said, "Yes, of course." But then I never heard from him again.

Then in January, I sent him an email: "Dennis, let's team up, and let's try that our institutions nominate us for the Nobel Prize." He was away. His secretary sent me a CV. He had promised to contact me; he never did. I said, "Okay, I'll try to get the Max Planck Society to nominate both of us." And then something terrible happened. I always get the nomination [proposal] for the Nobel Prize from the Nobel Society, and I had not really looked into it. Last year, nomination deadline was March 15. I know that exactly because somebody nominated me or wanted to nominate me. So I thought it was March 15 again [in 2003]. The president of

the Max Planck Society had agreed to nominate me and Dennis. And then, at the end of February, I talked to somebody and asked him if he would help me write the nomination proposal for me and for Dennis. He called back and said, "Well, this is a little late because the deadline was February 1." The culmination of this whole drama will be [may be?] that this year the Nobel Prize will be given to the Gleevec people, plus Dennis Slamon, maybe.

[End Tape 4, Side B]
[Begin Tape 5, Side A] ##

Genentech as a Model for the Industry

Hughes: We are running out of time. So I will ask you: Do you think that Genentech, being the first and being successful, served as a model for the biotech companies that followed—in science, intellectual property, the business aspects?

Ullrich: Definitely, yes. Genentech set certain standards which were looked at as prime examples of how one should do it. One should look at the whole California small-company culture, Silicon Valley included. It's so funny, really, when you look back--Swanson or the management thought that they should train their scientists a little bit in management skills and so on. So they sent us to management courses. It was not very successful. It included descriptions of company models that Genentech was aspiring to. But Genentech was clearly driven by internal forces and could not fit into any sort of commonly known model.

We had once an offsite meeting to which Swanson had invited the chairman of a Silicon Valley company. Either it was Intel or a company like that, very successful at that time. The CEO was telling the story of how this company was founded and how it developed so successfully. It all sounded very similar to Genentech, including sort of a failure at the end, sort of the downfall of the company. We [the Silicon Valley company] were so arrogant; we thought we were the greatest; we were the best. We even had a company song that said, "We are so wonderful, we are fantastic." Then for some reason, something happened. This was of course also a competitive field--chip manufacturing and all that. Some failure occurred, I don't know exactly what it was. In one day, their stock crashed by sixty or seventy percent. And they couldn't understand how this could have happened because they were the greatest and the best.

The circumstances of my leaving Genentech were very similar to that. Everyone thought it was wonderful and so on. In '88, tPA was submitted to the FDA for approval. And then, in April, there was a very important pre-approval hearing with all these experts there [at the FDA panel]. The company had to present its case, clinical trial results, and so on. The guy who was heading the clinical trials was an M.D., Eliot Grossbard, and he was completely fanatic about this project.

There was this FDA panel, and I was brought from Europe. I came back on April 4, I think it was, and I arrived at the airport, went through immigration, showed my green card. The INS officer always asks, "Where do you work?" So I said, "Genentech," and she said, "I don't think you want to come back." She pulls this newspaper out from under the desk, shows me a big headline--I don't know the [exact] words anymore: "Big disaster at Genentech. The FDA panel does not approve the drug," and so on. And stock has fallen like fifty percent.

I had not [yet] accepted this job offer that I had from Max Planck Society. But at that moment I thought, "Okay, this is crazy. I cannot allow that. I am in a company of 1700 or 1800 people, and one person in that company can make a major mistake, and the whole company collapses. And my life is completely connected to this place. So, I have to leave." That's when I decided to leave, so I told them maybe a week later. I left in June, and they were very generous. I could still wind down my lab and finish projects, and they allowed me to take everything with me, just like the old story, clones and materials. And I was a consultant with them. So, I took the next step of my life, and that was fourteen years ago.

More on Sugen and Two Subsequent Companies

Hughes: And the next step you consider to be Sugen?

Ullrich: Then it's Sugen, of course.

Hughes: Did you have Sugen in your mind when you left Genentech?

Ullrich: No, but it became very clear because I continued in this line of investigation of cancer, oncogenes, possible targets for drug development [at Max Planck]. It became very clear that at Max Planck I could not translate these ideas into action. I was disappointed by German companies. German pharmaceutical companies really were not interested, or they were afraid, or I didn't make any productive contacts with them, so there was no cooperation. I at that time was a very close friend with Joseph Schlessinger. It was clear that one had to start a company in order to exploit the potential of this field of research we were in. At the end of the '80's it was very clear through HER2 and other examples that this field had a high potential of producing interesting leads. And the whole idea of target-specific drug development--I had that idea in '83 when the EGF receptor story broke. It was a good basis. So we started looking around for investors. The NYU [New York university] intellectual property transfer office was very supportive in that because Joseph Schlessinger was at NYU. That's how we met Stephen Evans-Freke, sort of a self-made venture capitalist. And that's how Sugen was born.

Hughes: What year?

Ullrich: In August ’91. We started looking already in ’90, talked to some people who were interested but didn’t move fast enough. With this guy, Stephen Evans-Freke, we met him maybe in April 2001, and August, we signed a contract. And in 2002 facilities were open, and it was a big success.

Hughes: If you hadn’t had this fiat from Genentech about working with HER2, would HER2 have been wrapped into what you hoped to do at Sugen?

Ullrich: Well, if they had given the green light to that one, I would have stayed at Genentech.

Hughes: So there wouldn’t have been a Sugen.

Ullrich: Sugen was not working in the direction of antibodies but wanted to develop small molecule inhibitors. Genentech was so disinterested in this HER2 project that they didn’t patent anything. Even though I urged them to file patents, they never patented anything. After I had left, there were patents filed on the use of antibodies, etc. So, there are about five patents on which I am the inventor but not in the early times when it should have been done. The HER2 sequence was not patented, the antibodies in the beginning were not patented. Dennis and I were urging Genentech but they were not interested..

Hughes: Was that because they didn’t see the potential or that their focus was on other things? TPA for example was coming along.

Ullrich: Your guess is as good as mine.

Hughes: When you were setting up Sugen, how much was Genentech in your mind about what you wanted to achieve and not achieve with this company you were creating?

Ullrich: Well, I had no bad feelings about Genentech, but I thought I knew very well what was done not so well at Genentech. I wanted to create a company that copied all the good things at Genentech and added a few things that were [improvements].

Hughes: Can you give me an idea of what those things were?

Ullrich: Well, the things were obviously doing good science, publishing. People management was probably not ideal at Genentech, at least in the later times. People should have freedom and should be encouraged to have their own ideas and go after their own ideas. People should be rewarded justly for what they contribute. It’s very simple, really. But it’s not so easy to do. Even as a founder,

you don't have that much influence. Once a company is larger than fifty people; your influence declines progressively.

After Sugen, I founded two more companies, and I'm having the same experience again. One is now over a hundred people. Even though I'm on the board, I don't have any major influence on what they're doing.

Hughes: And what is that company?

Ullrich: That company develops drugs against infectious diseases, on the same principle—target driven-- because it's also clear that infectious diseases use mechanisms [very similar to] cancer to re-program a cell. And infectious agents cause the infectious disease symptoms that way, so it's very analogous to cancer. So that's that company. And then I saw started a follow-up to Sugen, a cancer company, one and a half years ago. Even though it's almost perfectly set up, the times are so terrible, finding money is absolutely crazy—so difficult. And that's my worry now. I have to help this company survive.

Hughes: What is the name of it?

Ullrich: U3 Pharma.

Hughes: Meaning what?

Ullrich: "U" for Ullrich:. And my third company. [laughter]

Hughes: Do you consider yourself now more of a businessman than a scientist?

Ullrich: Certainly more than I would have ever thought. And I enjoy it. There are some elements in that activity that make it more real. You have people; you have to pay these people. If the company does not succeed, these people are out of work. It's a greater sense of responsibility compared to lab work. What I'm doing at Max Planck is playing around.

Hughes: Are you still at the bench?

Ullrich: No.

Ullrich: So, I really am seriously [thinking of] leaving Max Planck. If this cancer company survives, then I would like to get a lab there and go back to the bench and actually do a little small-scale science again.

Contributions

Hughes: Well, there's always an on-going story. But I will end today with a question: what do you consider to be your most important contribution?

Ullrich: [pause] Well, I think my entire scientific work. It was important for me and important for many other people that I was stubborn and continued on the track that was predestined for me by truffle nose, by my scientific instinct. I'm not a scientist like most of the people. There are many types of scientists, as you know, I'm sure. There are the bookkeeper type of scientists, administrator scientists, that pick one project, and then they do every little detail, every aspect of it. That's not my style. I've started many projects, always within a very broad range of subjects, always receptor tyrosine kinases and cancer. But this is a huge field, so I've had excursions within this field to this and that and abandoned them. Usually it depends on people. I'm probably not a good strategist and manager, which you have to be, should be, in science. So, some projects probably sort of died because the person worked on it had left, and I didn't find a new person to take up this project. When you look back at everything that I have published, there are many interests, many discoveries. But the follow-up is probably not done as it could have been, and mostly other people have already picked things up and pursued them. So, overall, I'm proud that I stayed still within that certain range and made several seminal discoveries. I'm very happy about and proud of the HER2 and EGF receptor projects, and I would be very sad if someone else would get the exclusive credit for it. Overall, I think I always have had the right instinct where something interesting was evolving. I was in many areas, always on the front line, and that's a good feeling, even when not many people respect and realize that. But I know it.

Hughes: You know it.

Ullrich: I don't know what the single most important contribution is. Sort of the whole thing.

Hughes: I thank you. [End of interview]

##

Transcribers: Michael J. McArdle and Linda Le
Production Editor: Gerald Stone

TAPE GUIDE--Axel Ullrich

CURRICULUM VITAE—Axel Ullrich

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Telefax: +49 89 8577 866
E-mail: ullrich@biochem.mpg.de

Born: October 19, 1943 in Lauban/Schlesien, Germany
Citizenship: Germany

Education

4/64 - 4/71	University of Tübingen, Germany - Diploma in Biochemistry
5/71 - 3/72	University of Münster, Germany, Institute of Biochemistry
4/72 - 9/75	University of Heidelberg, Germany - Ph.D. Molecular Genetics

Fellowships

1972-1975:	Recipient of a fellowship for graduate studies at the Institute of Molecular Genetics (University of Heidelberg)
1975-1977:	Recipient of a postdoctoral fellowship from the "Deutsche Forschungsgemeinschaft"

Professional Appointments

05/71 - 03/72	Assistant Biochemist - Institute of Biochemistry, University of Münster, Germany
10/75 - 09/77	Postdoctoral Fellow - University of California, Department of Biochemistry and Biophysics, San Francisco, USA.
10/77 - 12/78	Assistant Research Biochemist - University of California, San Francisco, USA.
01/79 - 10/84	Senior Scientist - Genentech, Inc., South San Francisco, USA.
11/84 - 06/88	Staff Scientist - Genentech, Inc., South San Francisco, USA.
12/88 - present	Director - Department of Molecular Biology, Max-Planck-Institut für Biochemie, Martinsried, Germany
1999	Managing Director Max-Planck-Institut für Biochemie
07/04 - present	Visiting Scientist and Research Director of the Singapore Oncogenome (SOG) and OncoDrug Development (SODD) Projects, Centre for Molecular Medicine(CMM)), Agency for Science, Technology and Research (A*Star), Singapore

Biotechnology Activities

09/91 - 08/99	Founder, Consultant and Chief Scientist of SUGEN, Inc., U.S.A.
09/91 - 08/99	Member Board of Directors and Scientific Advisory Board, SUGEN, Inc., South San Francisco, U.S.A.
1992 - 1996	Advisory Board, Garching Innovation GmbH, Munich, Germany
11/96 – 2004	Chairman Advisory Board, Garching Innovation GmbH, Munich,
1996 – 2002	Science Advisory Board, Bionomics Ltd., Adelaide, Australia
01/1998	Founder of Axxima Pharmaceuticals AG, Martinsried, Germany
01/98 – 12/2004	Board of Directors, Axxima Pharmaceuticals AG, Munich, Germany
01/99 – 12/1999	Co-Chairman Clinical Science Advisory Board, SUGEN/Pharmacia, U.S.A.
08/99 – 09/2002	Board of Directors, BioImage A/S, Copenhagen, Denmark
09/99 – 03/2003	Science Advisory Board, SUGEN/Pharmacia, U.S.A.
2000 – 2004	Senior Advisor, TVM, Munich, Germany
2000 – 2004	International Advisory Council (IAC), Agency of Science, Technology and Research (A*Star), Singapore
01/01 – 05/2003	Science Advisory Board, Replicor, Montreal, Canada
09/01	Founder U3 Pharma AG, Martinsried, Germany
2001 – present	Chairman of the Board of Directors, U3 Pharma AG, Martinsried, Germany
11/01 – present	Board of Directors, Cryptome Pharmaceuticals Ltd, Melbourne, Australia
06/02 – 12/2003	Science Advisory Board, AxCell Biosciences, Newtown, U.S.A.
09/02 – 08/2003	Chairman Science Advisory Board, BioImage A/S, Denmark
07/03 – present	Advisory Board, Boehringer-Ingelheim, Ingelheim, Germany
03/04 - present	Board of Directors, Signature Diagnostics AG, Berlin, Germany

Science Advisory Boards

1991 - 1995	Science Advisory Board, Hagedorn Research Institute, Denmark
1992 - 2000	Vice Chairman Advisory Board, Hans Knöll Institut, Jena, Germany
1995 - 2002	Science Advisory Board, The Wistar Institute, Philadelphia, USA
08/96 - present	Founder and Vice Chairman of Academic Board - Cooperation Laboratory for Biological Signal Transduction Research, Second Military Medical University, Shanghai, China
07/97 – present	Science Advisory Board, BioM AG, Martinsried, Germany
2001 – 2003	Science Advisory Board, RZPD (German Resource Center for Genome Research), Berlin, Germany
2001 - present	Science Advisory Board, Biomedicum, Helsinki, Finland
05/03 – present	One-North Resource Advisory Panel, JTC Corporation and Ministry for the Environment, Singapore
08/03 - present	Board of Trustees, Max-Delbrück-Centre for Molecular Medicine, Berlin, Germany
08/03 – 12/04	Member of an International Panel for the Planning of a Research-Intensive University, Ministry of Education, Singapore
06/05 – present	Board of Directors, S*Bio Corporation, Singapore
12/03 – present	Member of the Scientific Committee of Genoma Espana, Madrid, Spain

Memberships in Scientific Societies

Academia Europaea
The American Society for Cell Biology
Gesellschaft für Biochemie und Molekularbiologie e.V.
American Association for Cancer Research
International Union Against Cancer (UICC)
Deutsche Krebsgesellschaft
International Life Science Forum
American Association for the Advancement of Science (AAAS)
Elected Member of the Deutsche Akademie der Naturforscher Leopoldina
Elected Member of the American Academy of Arts & Sciences

Extramural Responsibilities

Editorial Board, *Growth Factors*
Editorial Board, *Molecular Brain Research*
Editorial Board, *Receptors and Channels*
Editorial Board, *Journal of Cellular Physiology*
Editorial Board, *Cancer Genomics & Proteomics*
Advisory Board, *Molecules and Cells*
Editorial Board, *Molecular Cancer Research*

Honors and Awards:

1987	Paul Langerhans Medal of the German Diabetes Society
1987	John W. Cline Memorial Lecturer (sponsored by the American Cancer Society), UCLA
1987	First Annual Ray A. and Robert L. Kroc Lecture, University of Massachusetts, USA
1988	Berthold Medal of the German Society for Endocrinology
1990	Member of the European Molecular Biology Organization
1990:	Mildred Scheel Memorial Lecture, Modern Trends in Human Leukemia Conference, Hamburg, Germany
1991	Prix Antoine Lacassagne from La Ligue Nationale Française Contre le Cancer, Paris, France
1996	11th Annual Ray A. and Robert L. Kroc Lecture, Joslin Diabetes Center, Boston, Massachusetts, USA
	Honorary Professor - Second Military Medical University, Shanghai, China
1996-98	Visiting Professor, Académie de Paris, Sorbonne, Paris, France
1997	Gold Medal and "XXII Lorenzini" Annual Lecture, Fondazione Giovanni Lorenzini, Medical Science Foundation, Bari, Italy
1998	German Cancer Prize of the German Cancer Society
1999	Ludwig Heilmeyer Lecture, The International Society of Gastroenterological Carcinogenesis, Ulm, Germany
2000	Honorary Professor, University of Tübingen, Germany
	Bruce F. Cain Memorial Award, American Association for Cancer Research

2000	Elected Member of the Deutsche Akademie der Naturforscher Leopoldina
2001	Busenfreund, a prize awarded by mamazone – women and science against breast cancer e.V.
2001	Robert-Koch Prize of the Robert-Koch-Foundation International Fellow , Garvan Institute of Cancer Research, Sydney, Australia
2002	Virchow Lecture, University of Würzburg, Germany IJC-Meyenburg Lecture, University of Heidelberg, Germany
2003	King Faisal International Prize for Medicine, King Faisal Foundation, Saudi Arabia Meyer-Schwickerath Lecture, Society of Medical Science, Essen, Germany
2005	Warburg Medal, Society for Biochemistry and Molecular Biology, Germany Recipient of the Marshall School "European BioBusiness Leadership Award" Elected Member of the American Academy of Arts & Sciences

Major Scientific Achievements

Insulin

First cloning of preproinsulin cDNA leading subsequently to the development of the first gene-technology-based therapeutic protein product by Genentech, Inc. and Eli Lilly Corp. "Humulin"

Ullrich, A., Shine, J., Chirgwin, J., Pictet, R., Tischer, E., Rutter, W.J., and Goodman, H.M. (1977) Rat insulin genes: Construction of plasmids containing the coding sequences. *Science* 196, 1313-1319.

Sures, I., Goeddel, D., Gray, A., and Ullrich, A. (1980) Nucleotide sequence of human preproinsulin complementary DNA. *Science* 208, 57-59.

Growth Factors

Elucidation of primary structures, by cDNA cloning, of the precursor proteins for EGF, NGF IGF-1, and IGF-2.

Gray, A., Dull, T.J., and Ullrich, A. (1983) Nucleotide sequence of epidermal growth factor cDNA predicts a 128,000-molecular weight protein precursor. *Nature* 303, 722-725.

Ullrich, A., Gray, A., Berman, C., and Dull, T.J. (1983) Human beta-nerve growth factor gene sequence highly homologous to that of mouse. *Nature* 303, 821-825.

Ullrich, A., Berman, C.H., Dull, T.J., Gray, A., and Lee, J.M. (1984) Isolation of the human insulin-like growth factor I gene using a single synthetic DNA probe. *EMBO Journal* 3, 361-364.

Dull, T.J., Gray, A., Hayflick, J.S., and Ullrich, A. (1984) Insulin-like growth factor II precursor gene organization in relation to insulin gene family. *Nature* 310, 777-781.

Growth Factor Receptor Tyrosine Kinases

Cloning and primary structure elucidation of the first signal transducing cell surface protein, the EGF-receptor. First complete characterization of a protooncogene (c-erbB) product with known biological function. Discovery of EGFR gene amplification in cancer cells.

Ullrich, A., Coussens, L., Hayflick, J.S., Dull, T.J., Gray, A., Tam, A.W., Lee, J., Yarden, Y., Libermann, T.A., Schlessinger, J., Downward, J., Mayes, E.L.V., Whittle, N., Waterfield, M.D., and Seeburg, P.H. (1984) Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells. *Nature* 309, 418-425.

Cloning and characterization of receptors for insulin (IR))], PDGF, IGF-1, CSF-1 and SCF. Elucidation of oncogenic mutations in CSF-1- and SCF (kit) receptors. All but the IR currently serve as targets for cancer drug development.

Ullrich, A., Bell, J.R., Chen, E.Y., Herrera, R., Petruzzelli, L.M., Dull, T.J., Gray, A., Coussens, L., Liao, Y-C., Tsubokawa, M., Mason, A., Seeburg, P.H., Grunfeld, C., Rosen, O.M., and Ramachandran, J. (1985) Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes. *Nature* 313, 756-761.

Yarden, Y., Escobedo, J.A., Kuang, W-J., Yang-Feng, T.L., Daniel, T.O., Tremble, P.M., Chen, E.Y., Ando, M.E., Harkins, R.A., Francke, U., Fried, V.A., Ullrich, A., and Williams, L.T. (1986) Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors. *Nature* 323, 226-232.

Ullrich, A., Gray, A., Tam, A.W., Yang-Feng, T., Tsubokawa, M., Collins, C., Henzel, W., Le Bon, T., Kathuria, S., Chen, E., Jacobs, S., Francke, U., Ramachandran, J., and Fujita-Yamaguchi, Y. (1986) Insulin-like growth factor I receptor primary structure: Comparison with insulin receptor suggests structural determinants that define functional specificity. *EMBO Journal* 5, 2503-2512.

Coussens, L., Van Beveren, C., Smith, D., Chen, E., Mitchell, R.L., Isacke, C.M., Verma, I.M., and Ullrich, A. (1986) Structural alteration of viral homologue of receptor proto-oncogene fms at carboxyl terminus. *Nature* 320, 277-280.

Yarden, Y., Kuang, W-J., Yang-Feng, T., Coussens, L., Munemitsu, S., Dull, T.J., Schlessinger, J., Francke, U., and Ullrich, A. (1987) Human proto-oncogene c-kit: A new cell surface receptor-tyrosine kinase for an unidentified ligand. *EMBO Journal*. 6, 3341-3351.

Target-specific Cancer Therapy

Discovery of the putative growth factor receptor HER2/neu and demonstration of its major role in mammary and ovarian carcinoma progression. Development of HER/neu-specific monoclonal antibody 4D5, which was subsequently developed to the first gene-based , target-specific anti-oncogene cancer therapeutic -Herceptin- (Genentech Inc. / Hoffmann-La Roche) and is available to breast cancer patients since 11/1998.

In 2005 results of a multi-center trial (HERA) which were reported at ASCO demonstrated a major benefit for HER2 positive breast cancer patients in adjuvant therapy preventing tumor recurrence in 46% of the probands.

Coussens, L., Yang-Feng, T.L., Liao, Y-C., Chen, E., Gray, A., McGrath, J., Seeburg, P.H., Libermann, T.A., Schlessinger, J., Francke, U., Levinson, A., and Ullrich, A. (1985) Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 230, 1132-1139.

Slamon, D.J., Clark, G.M., Wong, S.G., Levin, W.J., Ullrich, A., and McGuire, W.L. (1987) Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235, 177-182.

Slamon, D.J., Godolphin, W., Jones, L.A., Holt, J.A., Wong, S.G., Keith, D.E., Levin, W.J., Stuart, S.G., Udove, J., Ullrich, A., and Press, M.F. (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244, 707-712.

Hudziak, R.M., Lewis, G.D., Winget, M., Fendly, B.M., Shepard, H.M., and Ullrich, A. (1989) p185HER2 monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor. *Mol. Cell. Biol.* 9, 1165-1172.

Patents:

Method of Treating Tumor Cells by Inhibiting Growth Factor Receptor Function; Hudziak, R., Shepard, H.M., and Ullrich, A. (WO 89/06692; Jul 27, 1989)

In Vivo Tumor Detection Assay
(U.S. Patent 5,720,937; Feb 24, 1998)
Hudziak, R., Ullrich, A., Fendly, B.M. (1998)

HER2 Extracellular Domain
(EP 0 474 727 B1, Jul 23, 1997, U.S. Patents 6,015,567; Jan 18, 2000, 6,333,169 B1; Dec 25, 2001)
Hudziak, R., Shepard, H.M., Ullrich, A.

Monoclonal Antibodies Directed to the HER2 Receptor
(U.S. Patents 5,677,171; Oct 14, 1997, 5,720,954, Feb 24, 1998, 5,725,856; March 10, 1998, 5,770,195; Jun 23, 1998, 5,772,997; Jun 30, 1998, 6,165,464, Dec 26, 2000, 6,387,371 B1, May 14, 2002, 6,399,063 B1; Jun 4, 2002)
Hudziak, R., Shepard, R, M., Ullrich, A., Fendly, B.M.

Angiogenesis and Anti-Angiogenesis Therapy

Identification of Flk-1/VEGFR2 as the critical receptor for the development of the vascular system and for tumor angiogenesis resulting in the development of the target-specific (Flk-1/VEGFR2) anti-angiogenic drug (SU5416) and the multi-targeted drugs SU6668 and SU11248 by SUGEN, Inc. for the treatment of various cancer indications. SU11248 (SUTENT) was submitted in August 2005 (Pfizer) to the FDA for approval for the treatment of Gleevec-resistant Gastrointestinal Stromal Tumors (GIST). Phase III trials are ongoing for therapy of renal cell carcinoma and other indications. SU11248 is the first "designed" multi-targeted cancer drug (Pfizer)

Millauer, B., Wizigmann-Voos, S., Schnürch, H., Martinez, R., Møller, N.P.H., Risau, W., and Ullrich, A. (1993) High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. *Cell* 72, 835-846.

Millauer, B., Shawver, L.K., Plate, K.H., Risau, W., and Ullrich, A. (1994) Glioblastoma growth inhibited in vivo by a dominant-negative Flk-1 mutant. Nature 367, 576-579.
Millauer, B., Longhi, M.P., Plate, K.H., Shawver, L.K., Risau, W., Ullrich, A., and Strawn, L.M. (1996) Dominant-negative inhibition of Flk-1 suppresses the growth of many tumor types in vivo. *Cancer Res.* 56, 1615-1620.

Strawn, L.M., McMahon, G., App, H., Schreck, R., Kuchler, W.R., Longhi, M.P., Hui, T.H., Tang, C., Levitzki, A., Gazit, A., Chen, I., Kéri, G., Orfi,, L., Risau, W., Flamme, I., Ullrich, A., Hirth, K.P. and Shawver, L.K. (1996) Flk-1 as a Target for Tumor Growth Inhibition. *Cancer Res.* 56, 3540-3545.

Fong, T.A.T., Shawver, L.K., Sun, L., Tang, C., App, H., Powell, T.J., Kim, Y.H., Schreck, R., Wang, X.Y., Risau, W., Ullrich, A., Hirth, K.P., and McMahon, G. (1999) SU5416 is a potent and selective Inhibitor of the Vascular Endothelial Growth Factor Receptor (Flk-1/KDR) that Inhibits Tyrosine Kinase Catalysis, Tumor Vascularization, and Growth of Multiple Tumor Types. *Cancer Res* 59 (1), 99-106.

Laird, A.D., Vajkoczy, P., Shawver, L.K., Thurnher, A., Liang, C., Mohammadi, M., Schlessinger, J., Ullrich, A., Hubbard, S.R., Blake, R.A., Fong, A.T., Strawn, L.M., Sun, L., Tang, C., Hawtin, R., Tang, F., Hirth, K.P., McMahon, G., and Cherrington, J. (2000) SU6668 is a potent Anti-Angiogenic and Anti-Tumor Agent which Induces Regression of Established Tumors. *Cancer Res.* 60 (15), 4152-4160.

Patents:

Flk-1 Is a Receptor for Vascular Endothelial Growth Factor
(U.S. Patent 5,851,999; Dec 22, 1998, EP 0 669 978 B1; Apr 23, 2003))
Ullrich, A., Risau, W., Millauer, B. (1998)

Use of Organic Compounds for the Inhibition of Flk-1 Mediated Vasculogenesis and Angiogenesis
(U.S. Patent 6,177401 B1; Jan 23, 2001)
Ullrich, A., Risau, W., Millauer, B.

Cellular Signaling Network

Discovery and characterization of the G-protein-coupled EGF Receptor Transactivation pathway in normal and cancer cells. Demonstration that physiological factors like LPA, Angiotensin II, Endothelin and others maybe involved in cancer progression.

Daub, H., Weiss, F.U., Wallasch, C. and Ullrich, A. (1996) Role of transactivation of the EGF receptor in signalling by G-protein-coupled receptors. Nature 379, 557-560.
Zwick, E., Daub, H., Aoki, N., Yamaguchi-Aoki, Y., Tinhofer, I., Maly, K. and Ullrich, A. (1997) Critical Role of Calcium-dependent Epidermal Growth Factor Receptor Transactivation in PC12 Cell Membrane Depolarization and Bradykinin Signaling. *J.Biol.Chem.* 272, 24767-24770

Prenzel, N., Zwick, E., Daub, H., Leserer, M., Abraham, R. Wallasch, C. and Ullrich, A (1999) EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF. *Nature,* 402, 884-888.

Gschwind, A., Hart, S., Fischer, O.M., and Ullrich, A. (2003) TACE Cleavage of Proamphiregulin Regulates GPCR-induced Proliferation and Motility of Cancer Cells. *EMBO Journal.* 22 (10), 2411-2421.

Patents:

Use of Proteinase Inhibitor in Order to Inhibit the Cleavage of Growth Factor Precursor
(Australian Patent 779 298; May 12, 2005, WO 01/12182 A1)
Ullrich, A., Prenzel, N., Daub, H., Zwick-Wallasch, E. (1999)

Use of EGFR Transactivation Inhibitors in Human Cancer
(WO 03/075947 A1, PCT/EP 03/02361)
Ullrich, A., Schäfer, B., Fischer, O., Gschwind, A., Leserer, M. (2003)

Inhibition of TACE or Amphiregulin for the Modulation of EGF Receptor Signal Transactivation
(WO 2004/073734 A1, PCT/EP 2004/001691)
Ullrich, A., Gschwind, A., Hart, S.

Discovery of the FGF Receptor 4 Germ Line 388Arg Allele

Demonstration of the prognostic significance of this SNP for breast- and colon cancer patients. Establishment of FGFR4 as intervention target for cancer therapy.

Bange, J., Prechtel, D., Cheburkin, Y., Specht, K., Harbeck, N., Schmitt, M., Knyazeva, T., Müller, S., Gärtner, S., Sures, I., Wang, H., Imyanitov, E., Häring, H.U., Knyazev, P., Iacobelli, S., Höfler, H. and Ullrich, A. (2002) Cancer progression and tumor cell motility are associated with the FGFR4 Arg388 allele. *Cancer Research* 62, 840-847.

Streit, S., Bange, J., Fichtner, A., Ihrler, S., Issing, W., and Ullrich, A. (2004) Involvement of the FGFR4 Arg388 Allele in Head and Neck Squamous Cell Carcinoma. *Int. J. Cancer* 111, 213-217.
Patent:

Use of Inhibitors for the Treatment of Disorders Related to RTK Hyperfunction, Especially Cancer
(U.S. Patent 6,770,742 B1; Aug 3, 2004, EP 9900405, AU 756378 B2)
Ullrich, A., Bange, J., Knyazev, P.

Citation Ranking

According to *Science Watch* (Vol. 14, No. 5, 2003) Axel Ullrich ranks internationally at position five of most cited scientists during the 1983-2002 period with 58.395 citations. He is the most cited German and 3rd ranked European scientist during this period.

PATENTS

UCSF

Method for Producing Recombinant Bacterial Plasmids Containing the Coding Sequences of Higher Organisms
(U.S. Patent 4,440,859; Apr. 3, 1984)
Rutter, W.J., Goodman, M., Ullrich, A., Shine, J., Chirgwin, J., Pictet, R.

Recombinant Bacterial Plasmids Containing the Coding Sequences of Insulin Genes
(U.S. Patent 4,652,525; Mar 24, 1987)
Rutter, W.J., Pictet, R., Chirgwin, J., Goodman, H., Ullrich, A., Shine, J

Genentech

Insulin Receptor
(U.S. Patent 4,761,371; Aug 2, 1988)
Bell, J., Ramachandran, J., Ullrich, A.

Method of Detecting Truncated Epidermal Growth Factor Receptors
(U.S. Patent 4,933,294; Jun 12, 1990)
Waterfield, M.D., Schlessinger, J., Ullrich, A.

Receptor for Efficient Determination of Ligands and their Antagonists or Agonists
(U.S. Patent 5,030,576; Jul 9, 1991)
Dull, T., Riedel, H., Ullrich,A.

Human Nerve Growth Factor by Recombinant Technology
(U.S. Patent 5,169,762; Dec 8, 1992; 5,288,622; Feb 22, 1994)
Gray, A., Ullrich, A.

Improvements Relating to Growth Factors
(EP 0 171 407 B1; Nov 18, 1993)
Waterfield, M.D., Schlessinger, J., Ullrich, A.

Hybrid Receptors, Nucleic Acid Encoding them, their Preparation, and their Use in Determination of Ligands and their Antagonists and Agonists
(EP 0 244 221 B1, Jun 26, 1996)
Dull, T., Riedel, H., Ullrich,A.

Monoclonal Antibodies Directed to the HER2 Receptor
(U.S. Patents 5,677,171; Oct 14, 1997, 5,720,954, Feb 24, 1998, 5,725,856; March 10, 1998, 5,770,195; Jun 23, 1998, 5,772,997; Jun 30, 1998, 6,165,464, Dec 26, 2000, 6,387,371 B1, May 14, 2002, 6,399,063 B1; Jun 4, 2002)
Hudziak, R., Shepard, R, M., Ullrich, A., Fendly, B.M.

HER2 Extracellular Domain
(EP 0 474 727 B1, Jul 23, 1997, U.S. Patents 6,015,567; Jan 18, 2000, 6,333,169 B1; Dec 25, 2001)
Hudziak, R., Shepard, H.M., Ullrich, A.

In Vivo Tumor Detection Assay
(U.S. Patent 5,720,937; Feb 24, 1998)
Hudziak, R., Ullrich, A., Fendly, B.M. (1998)

Preparation of Human IGF and EGF via Recombinant DNA Technology
(U.S. Patents 6,331,414 B1; Dec 18, 2001, 6,331,609 B1; Dec 18, 2001)
Lee, J., Ullrich, A.

A Method for Culturing Recombinant Cells
(U.S. Patents 6,235,498 B1; May 22, 2001; 6,399,331 B2; Jun 4, 2002)
Mather, J.P., Ullrich, A.

Method of Treating Tumor Cells by Inhibiting Growth Factor Receptor Function
(WO 89/06692; Jul 27, 1989)
Hudziak, R., Shepard, H.M., Ullrich, A.

Max-Planck-Institut für Biochemie

Verfahren zur Diagnose von nicht-Insulin-abhängigem Diabetes mellitus
(DE 41 14 365 C2)
Process for Diagnosing Non-Insulin-Dependent Diabetes Mellitus
(U.S. Patent 5,719,022; Feb 17, 1998))
Ullrich, A., Seedorf, L., Häring, H.U.,

Extracellular Signal-Regulated Kinase, Sequences, and Methods of Production and Use (Australian Patent 682506; U.S. Patents 5,459,036; Oct 17, 1995, 6,579, 972B1; Jun 17, 2003)
Ullrich, A., Lechner, C., Møller. N.P.H.

PTP-S31: A Novel Protein Tyrosine Phosphatase
(U.S. Patents 5,585,233; Dec 17, 1996, 6,492,495 B1, Dec 10, 2002)
Ullrich, A. , Møller, N.P.H., Møller, K.,

Verfahren zur Aktivitätsbestimmung von Phosphotyrosinphosphatasen und zur Identifizierung von Effektoren davon
(German Patent DE 44 39 662 C2, Oct 2, 1997, EP 0 791 072 B1; May 17, 2000)
Ullrich, A., Böhmer, F.D., Böhmer, S.A., Obermeier, A.

Recombinant DNA Encoding CCK-2, a Receptor Tyrosine Kinase
(U.S. Patent 5,677,144, Oct 14, 1997, EP 0 090 315 B1; May 25, 2005)
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