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University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

Michael S. Urdea, PhD:

NUCLEIC ACID CHEMISTRY AT CHIRON CORPORATION

Interviews conducted by
Sally Smith Hughes
in 1992

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Michael S. Urdea, circa 2005, photo courtesy of Michael Urdea

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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.

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University of California, Berkeley
November 2005

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Biographical Sketch

Mickey Urdea received a BS degree, magna cum laude, in biology and chemistry from Northern Arizona University in 1974. He obtained his PhD in biochemistry from Washington State University in 1979 under the direction of J. Ivan Legg focusing on metals in enzymology. His thesis project involved the synthesis of a substitution inert cobalt (III) complex of the enzyme, carboxypeptidase A, which won him first place in the first Oly Gold Research Award at WSU. He continued his education in biochemistry at the University of California in San Francisco as a National Institutes of Health Postdoctoral Research Fellow in the laboratory of William J. Rutter. Mickey switched fields during his postdoctoral fellowship when he studied chemical synthesis of nucleic acids and molecular biology.

In 1980, Mickey left UCSF to begin the company BioPolymers with Dr. Rutter, which in 1981 became part of Chiron Corporation in Emeryville, California. From 1981 to 1995 Mickey served Chiron consecutively as Scientist and Senior Scientist; Associate Director (for Research) and then Director of Nucleic Acid Chemistry; and Vice President, Research & Development, Nucleic Acid Systems. He was the first employee at Chiron to move from Scientist to Vice President. Initially, he began the DNA synthesis laboratory at Chiron, and then moved into nucleic acid diagnostics.

The major emphasis of Mickey's research has been the development of quantitative methods for the detection of viruses in human blood samples. He and his colleague Brian Warner developed a method called branched DNA signal amplification (or bDNA) that resulted in the first commercial products for so-called "viral load' analysis, a concept developed by Mickey in 1985. This bDNA method now employed in FDA approved diagnostics products, is used to directly detect as few as 50 molecules of RNA in 1 milliliter of blood.

The first Chiron bDNA product was for hepatitis B virus (HBV) and was introduced in 1991. A test for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were introduced in 1992 and 1993, respectively. In each case, these tests were the first sensitive commercial method for quantitation of the target virus available to the clinical community, years ahead of quantitative PCR. Viral load assays are now considered the standard of care for therapy selection and monitoring for persons infected with HBV, HCV and HIV, the field pioneered by Mickey and his team at Chiron. In 1999, Mickey was presented with the AIDS Healthcare Foundation "Caregiver Award" for contributions to the field of HIV/AIDS treatment with his Chiron colleague David Chernoff, M.D.

In 1995, Mickey became Vice President, Nucleic Acid Diagnostics (NAD) and New Markers assuming responsibility for the viral load testing business of Chiron Diagnostics and for new diagnostics marker research for Chiron. This later responsibility involved overseeing the strategy and methodology to find new disease diagnostics that could be used to screen, diagnose and monitor patients with cancer, cardiovascular disease or infectious diseases. Two years later Dr. Urdea was named Senior Vice President, NAD and New Markers.

Following the merger of Chiron's Diagnostics unit with Bayer Diagnostics in 1998, Mickey became Senior Vice President for NAD and acting Chief Scientific Officer of Bayer Diagnostics. After leaving Bayer in February 2000, Mickey became a biotechnology consultant serving as advisor, scientific advisory board member, or board of director member for several firms involved in basic research tools, genomics, proteomics, genetics, diagnostics and therapeutics. From May of 2001 until July 2002, he was interim President of Quantum Dots, Inc. Mickey also works with many venture capital funds to assess the potential of new biotech business opportunities. In 2003, Mickey and his business partner Greg Went began Halteres Associates, a biotechnology consulting firm specializing in diagnostics, where Mickey is Managing Partner.

Mickey has published widely and developed numerous patented compounds, processes and devices. He has written or co-authored more than 185 publications and has been issued or applied for more than 100 patents.

Interview with Michael Urdea, PhD

Interview #1: October 7, 1992
[Tape 1, Side A]

Hughes: Dr. Urdea, would you start back with your education and how you got up to being employed at Chiron?

Urdea: Oh, my goodness. Well, I did my PhD work in Washington at Washington State University, which I finished up in 1979. At that time came down to do a postdoctoral fellowship with Dr. Rutter, and I changed my fields at that point from protein chemistry to nucleic acid chemistry. I learned right after I came into that laboratory how to synthesize DNA, by going to Purdue University and working for a fairly short time--a few months. I came back to Bill's laboratory and set up DNA synthesis for the first time there.

Hughes: And was that something that he prompted?

Urdea: Oh, yes, absolutely. That was the notion we had in my coming to his lab, was that I would go off and learn this technology and bring it back and set it up at that lab. At that point, DNA synthesis was not something routinely done in many laboratories. It was before the advent of automated instruments, and before the advent of some of the chemistries that have been absolutely essential in most of the technology that has been developed in biotechnology.

At that time we were doing what was called triester chemistry. It took one person approximately two weeks to make two fragments of ten to fifteen nucleotides--full-time work, very difficult days of processing, whereas today, one person can make between four and ten sequences on an automated DNA synthesizer a day. So it's become a commodity as opposed to a research area. But at that point I was making DNA for, mostly for Bill's laboratory.

Hughes: Was that the insulin gene?

Urdea: At that time we were--he was passed the cloning of the insulin gene. We were looking at epidermal growth factor and some of the other growth factor genes. So I was in the laboratory for, let's see--a little less than a year, I believe, when we formed another company. The first company--in 1980, I think it must have been about September of 1980, and it was called Biopolymers, involved myself and Bill Rutter and fellow named C.K. Chang, and it was here in Emeryville. In fact, it was in the building that Cetus ended up in. There were some Cetus employees in the building at that time, but Cetus was spread out amongst, I think, thirteen separate locations in the Bay Area. They later consolidated in that building, so there are a lot of small buildings, entrepreneurial groups all in there. So Biopolymers was in there. We were right next door to Hana Biologics, as a matter of fact, which is how a

relationship came about with them. And one of the laboratories that was shared by Hana-Biopolymers group was the first laboratory that Chiron developed in.

Hughes: Now, what was the impetus for forming Biopolymers?

Urdea: Well, there was clearly a need for synthetic DNA in the research community, and there were very few sources for it. We were doing pretty well at it, able to make it for what we thought was a reasonable price, and the notion just came about that perhaps what we could do is sell DNA, and make some money, while also doing some improvements in the DNA synthetic methods with the money we might earn. So, it sounded very exciting to me and I decided to move into this industrial area.

Hughes: So you left the university entirely.

Urdea: Yes.

Hughes: Surely it wasn't just you, because at that point I can't imagine that Dr. Rutter had much day-to-day contact, did he?

Urdea: In the laboratory it was just me until I hired one fellow, and it's Jim Merriweather, who's on your list here. Jim and I were in school together at Washington, so he was an enterprising fellow, entrepreneurial like myself and decided that he'd like to join me. So he came down and it was just the two of us for quite some time. We worked our tails off . [laughter]

Hughes: I guess you did! Did you have business immediately?

Urdea: No, we started discussing things with several organizations. We ended up, though having a deal with Hana Biologics. As I mentioned, they were next door. We became part of Hana Biologics, and I don't recall the date of that, but it was either very late in 1980, or the beginning of 1981. The notion was that this could become part of the Hana series of products--would be DNA products that we would sell. And what we were making was what was called linkers. I'd devised a new way to make linkers that was a little bit different than what was out there at that time. A little more versatile, and so we were--our intention was to sell these things. We in fact never got to that, and--

Hughes: Where was the money coming from?

Urdea: C.K. Chang. He was the money and I guess I was the brawn and Bill the brains, something along those lines, I'm not sure. [laughter] That was how it was set up. So that got me into Emeryville here, and Emeryville was quite a place at that time, it was kind of the Wild West--these buildings that are out here are part of the Shell Oil development, and I believe in 1971 they left and consolidated all the research and development in Houston. So these old

research buildings just lay fallow here for many years until an enterprising fellow named Harold Chapman, I believe it was he who bought the buildings for a song and a dance, and started renting them out.

Zoning in the Bay Area was such that it was very difficult to find places to set up laboratories. Genentech had gone into South San Francisco. There were a few places in San Francisco, but the rent was very expensive, and Emeryville was here and the price was very good. So one of the things that we needed to do for organic chemistry was using fume hoods to get rid of the gases that were being produced during our processes. And these buildings were outfitted with laboratories with fume hoods in place, and they hadn't been turned on in quite a while in some cases, but they were completely functional, so it was a wonderful deal for us.

So not only was the rent cheap, but it had equipment that we needed to do this work. So that was--it was embarrassing that the buildings over there--we'd be in here at night, the halls weren't lit, we needed a flashlight to get around, and the lights were turned on in the labs we were in, so we could work in there, but when we left at night, there was no light at all. But one night I forgot my flashlight and bumped my nose against the wall in there, but I finally got out. [laughter] And there were people all over the place outside. There were--you'd hear gunshots and you'd see cars flying by and a poor fellow--Harold had his dogs out in our yard on the side here--I recall one of them being shot.

Hughes: So rough--

Urdea: So it was a rough area besides being pretty much vacant. And then a lot of people started recognizing this area was available and started moving in slowly but surely. And I knew this building, that the one that Chiron is in now, there weren't very many people in that one at all. I don't know if anyone was in it except for a few people that were living there. So, I knew that Chiron was about to be formed, it was--a matter of fact, Bill had called me into his office early on and asked me if I would like to participate in this new venture. And I said, "Well, we've got this Biopolymers thing going, and I don't think that I want to do that right now." And also, I was associated with the Hana Biologics group and I thought that looked very good.

Hughes: Was he meaning leave Biopolymers and come to Chiron? Because how could you do both?

Urdea: Yes, essentially leave and come.

Hughes: So he was willing to call an end to Biopolymers.

Urdea: Well, I don't recall him specifically saying that, but I think that that was the intent. We had quite a falling out with the people at Hana and I don't think

the relationship ended up being quite what we hoped for, so this was one way to deal with that.

Hughes: What did you expect of them?

Urdea: Of--

Hughes: Of Hana.

Urdea: Well, it was more a working relationship than just--we didn't hit it off real well, and the chemistry wasn't all that great between us and them. I think that was more the issue.

Hughes: So it was really supposed to be a cooperative, scientific endeavor.

Urdea: Yes, but also the kind of products that were being developed and how much money it was going to take--there were a lot of issues.

Hughes: Is it relevant to ask who was behind Hana?

Urdea: The key people were Charles Crocker, of the Crocker family, and then a fellow named David Rammler who had been at Syntex for many years, and was involved in setting up a variety of different companies, and then a fellow names Ken Yamasaki--who really was the founder of the company. And then he brought these two fellows in--but they were the three that were the most important here.

Hughes: And that was it? Were there more people?

Urdea: There were people, but they were the key individuals. Quite a few of the people that were at Hana at that time are now at Chiron. Kathy Steimer who's here, and many of the people in her laboratory were people from Hana. And it was not a sudden shift. Virtually all of them went off somewhere else, or something and then came back at one time or another to Chiron.

Hughes: And in turn did those Hana people originally come from the universities in the Bay Area?

Urdea: Some yes, some no. Kathy had been most recently in UC San Diego, I believe.

Hughes: So it wasn't--Chiron was so very much in the early days tied with UCSF. The tie wasn't quite so strong with Hana.

Urdea: No. Not at all. No. Yes, the early days of Chiron it was very much a UC San Francisco/UC Berkeley outfit.

Hughes: Did that cause problems? There was still--today I guess there's still some tension between the academic and the industry--particularly when you have virtually whole labs, large portions of labs anyway, moving into industry. Did that raise problems?

Urdea: I imagine it did, but I think that Bill was actually very good about discussing these issues with the university before he even set up Chiron. I wasn't privy to exactly what was going on, but what I understand of it, I think he did a much better job than people like Herb Boyer, or some of the others that went off and started companies, about taking into consideration the university. But after all, Bill built that department and he did not want to see it suffer, and I don't think it did suffer. In fact, if anything, it has been enhanced. There are still an awful lot of good people that went off to do academic positions and other types of work. Many people did come to Chiron and other biotechnology companies, and for a long time we were the supply of synthetic DNA and other materials back to the university, trying to help them out, and I think in the long term they're going to profit from the products that have been developed.

So, yes, it's a problem, always going to be--I think there was a lot of resentment from people that were at the university. Especially when they found out people in this were making more money than they were, and the stock, and all the other things. So, but I don't think it was as bad with Chiron as it may have been with some of the other companies. I may be wrong about that, but that was my impression. So as I mentioned, Bill had asked me to join this early on, and I pretty much turned it down. Not pretty much--I did turn it down. I said, "No. I'm not interested." And that's one of the last times I'll ever underestimate Bill. The truth of the matter was that I didn't think that he was going to be able to raise sufficient funds and get the commitment from enough people to do this, so I just wasn't willing to do it. But come several months later, I decided that that was by far the best thing to do. So I ended up joining the company.

Hughes: Now, how do you raise money?

Urdea: Well, I think you probably have to ask him that. But it pretty much is the interaction with Merck for the HBV vaccine, and that project was the impetus for Chiron's formation, and for a lot of the people that were thinking about doing other things, stayed with Chiron. One story that you need to get the picture on, that is quite amazing--and I think Pablo is probably the best person to talk to about it--is the Amgen versus Chiron situation in the early days. Have you heard much--?

Hughes: He told me a little bit about that. This is going to be "Amgen North."

Urdea: That's right. Exactly. And a lot of the people at Chiron are all going to be part of Amgen. And they were looking around for a place to go, and Bill got

this commitment from Merck and got virtually everyone who had originally intended to go to "Amgen North" to decide to come to Chiron instead. Very powerful lobbying program.

Hughes: Who were those people?

Urdea: The key people were probably Pablo, Graeme Bell, and Rob Halliwell. There were others involved--Leslie Rawls, I don't know who the others were that were involved, but those people were the key people. If Graeme, and Pablo, and Rob had decided to go to Amgen, it would have made it very difficult the formation of Chiron early on.

Hughes: What was convincing people that Chiron was a viable idea?

Urdea: I think that firstly it was precedent for these kind of companies being formed in the Bay Area, so we knew it could be done. That the plan to develop a vaccine for HBV made a lot of sense, that we really did have the technology necessary to develop the kinds of clones and expression systems. It seemed that we had the essential ingredients for a successful company, and they were unique ingredients. The yeast knowledge. Really a basic knowledge of growth factors and the genes and how to clone them. The technology of cloning and sequencing, and designing probes, and synthesizing probes, and all these kinds of things. We felt very comfortable with all of that. And we thought we knew how to fill the gaps that we knew remained, that had commitment from, for instance, people from the Jeremy Thorner's laboratory and Tony Brake was here; with how we're going to improve the yeast technology and expression systems, so I think confidence, knowledge that everybody knew how to work together, there was some money there, that there was a lot of potential. That was very attractive.

Hughes: And was the idea that vaccines would be at least one of the emphases of the company?

Urdea: Right from the beginning, absolutely.

Hughes: And was the assumption made that the yeast system would work for other vaccines?

Urdea: Yes.

Hughes: Which didn't necessarily prove to be the case.

Urdea: No. I think the one rule about any of these cloning and expression systems to me seems to be that there's no rule. One day maybe we'll understand better. I'm not an expert in that area, but to me you shouldn't just try everything until something works.

Hughes: And nobody, of course, knew at that stage, did they? Who also was working with yeast expression systems in those early days?

Urdea: Well, the Genentech group was working on it. They weren't putting as much emphasis on it as Chiron was. There were a lot of people in academics doing it. There's--I don't know when ZymoGenetics started, but certainly the group from the University of Washington, the Hall Group, and the people associated with that group were working very hard at that--and that ended up becoming part of an industrial group. So I would say that there was a lot of overlap. There was a lot of overlap between the people in Washington, people at UCSF, and then the various companies associated with it, and then Berkeley. Those were the key groups. And then there were so many people working on bacterial expression, and again, UC was a major player at that if not the leader--then scattered throughout the country, a lot of emphasis in the Harvard area, and Boston, which I think gave rise to a lot of the companies that sprang up back there.

Hughes: Now, when you moved over from Biopolymers, was there just the hepatitis B project going?

Urdea: When I came over, that was the main emphasis. There was a lot of work going on cloning those specific genes for growth factors, and what we wanted to do was synthesize genes. And at the time, 1981, was a time when a radical change took place in technology for DNA synthesis. A technology was developed called phosphite chemistry and soon after that what's called phosphoramidite chemistry. And these were much more versatile methods for synthesizing DNA, they permitted one person to make several pieces of DNA in one day. It was still very tedious, but you could do it, instead of these old triester methods. People had made genes by triester methods. Genentech's first gene, the somatostatin gene was made using that kind of chemistry. Well, it's just not worth it in my opinion. So we made a big effort to get this technology ourselves through this phosphite chemistry.

Hughes: Where did you go?

Urdea: Well, the group that had developed it was a group at the University of Colorado, Marv Caruthers's group, and what I did is I arranged to have one of his graduate students act as a consultant to us, and his name is Rick Fisher and Rick came and spent three days with us, and I'm sure he didn't think that we'd be able to get enough information in three days, but we really picked his brains. We recorded him, we took down everything, and we had it set up shortly after that.

Hughes: Really!

Urdea: Yes.

Hughes: To his amazement.

Urdea: I think to his amazement. I think more to Marv Caruthers's amazement because he's one of the founders of Amgen.

Hughes: Oh, is that so. Boy!

Urdea: One of the early people with Amgen--so, they lost--.

Hughes: Did he sort of regret that? [laughs]

Urdea: He's never told me that, but I'll bet you he does! [laughs]

Hughes: I don't see how he could help it.

Urdea: Yes. So we were really good at that chemistry within about six months. It took us quite a while, but still--

Hughes: Were you just working day and night?

Urdea: Oh, yes. Absolutely. So we wanted to synthesize genes, and the genes we picked were--really I think Bill's probably the one who picked it--epidermal growth factor was our first synthetic gene, and the IGF-1 and IGF-2.

Hughes: Do you know why you picked those genes?

Urdea: Well, they were the ones where it seemed there might be the clearest potential indication as a therapeutic. People knew the most about it and I think we knew the structures, that was also very important, that we knew what the sequence of the genes were.

Hughes: Which had been worked out at UCSF.

Urdea: No, not necessarily. In fact, I don't think either of those was. But we just--from the literature we know what they are. So we worked first on EGF. We worked very hard on that one. We synthesized it, cloned it, sequenced it by September 2, 1982. And I remember that because that was my thirtieth birthday! [laughs]

Hughes: Quite a celebration!

Urdea: And I thought to myself, "Gee whiz, I've got my first synthetic gene by the time I'm thirty years old--I'm very pleased with that."

Hughes: [laughs] I do think you would be!

Urdea: And then we went on to work with insulin-like growth factor-I, insulin-like growth factor-II gene. By the time we got done with those, we felt if we could make anything--which we could--I made the insulin gene by myself, and the other guys who were working, Guy Mullenbach, Phil Barr, Jim Merriweather they were all making their own genes too. We'd gotten so good at it that we could just go off and make whatever we wanted to.

And you know those were the days when I think biotechnology companies--everyone was thinking the same things. We all knew what the genes were that were going to be important or useful from the literature, and we had all come up in the technology pretty close to the same level. It was just a matter of time. So many of the patent applications you see from those days have dates of invention that are different by a week, or a few days, so this day-and-night working, and getting it done on time was the most important thing since there were a few groups all of which had the same technical capability.

Hughes: But you couldn't know exactly where they were in the process, could you?

Urdea: No, but we had a good guess. We pretty much knew what was going on in other places. Those were also before the days when most people knew that they shouldn't talk too much.

Hughes: So you had your connections.

Urdea: Yes, yes. Like my grandfather always told me--keep your friends close, but your enemies closer.

Hughes: That's good advice in this case. But you still didn't have a product.

Urdea: No.

Hughes: No. Is it the time now to talk about that EGF story, which I understand is still continuing, but it has some unique--

Urdea: It's still continuing. Yes. It--maybe Pablo is the better person to talk to you about where it went after that. What I did is I took it to the point where we had the synthetic gene, and we saw some preliminary evidence for expression in our collaborations, and then, this just took off in a lot of other areas, and mostly that stuff Pablo was pushing through, give you a good feeling for it.

Hughes: Yes. Because that eventually led to the ophthalmic branch, didn't it?

Urdea: Yes, as a matter of fact that has a major impact on whether we got into that area or not. But we have a lot of products, a lot of materials around that are from our early days, and they are our most important products. The insulin certainly is--that's been a major product for Chiron--more so than we

probably realized at the time. But a lot of these growth factors are not--not as great as we hoped they would be.

Hughes: Why would you be discouraged about the insulin being a product? I mean a good product.

Urdea: I think a lot of us--I personally thought that Eli Lilly had this whole thing wrapped up.

Hughes: But it didn't in Europe, did it?

Urdea: It clearly didn't. Well, not--in the entire world, no. Yes. And there were certainly better processes for making insulin than what Eli Lilly had had.

Hughes: Another thing that happens relatively early on is--ooh--5:15! [tape break] How much about this connection with Martin Marietta--and there was supposed to be some sort of biotech consortium. Do you remember talk about that?

Urdea: Oh, yes. Definitely. Martin Marietta was looking at this triumvirate of companies. And it was Molecular Genetics that was one of them in Minnesota. I think they're outside of Minneapolis. I don't even know if they still exist, quite frankly--another company called Native Plants in Utah and Chiron. I think that their notion was that they were focusing on very different kinds of applications--

Hughes: Sounds that way.

Urdea: --of biotechnology--plants, and I think Molecular Genetics was more dedicated toward agricultural applications, and then Chiron being very much focused on human therapeutics. And trying to look at possible synergies there, things that we had that another group could use, and etc. That was their intent, and they were willing to invest in the future. That was a very interesting time. There weren't a lot of us that had interaction with the other groups. I personally was not involved in any of the discussions with any of those other companies.

Hughes: Do you know how long that relationship lasted?

Urdea: I can't tell you. Years, but I don't remember when it stopped.

Hughes: Because Jarmalow--is that the way you pronounce his name, or is it Yormalow?

Urdea: Jarmalow.

Hughes: Jarmalow was--actually joined the Chiron board.

Urdea: Yes. We still see him. He consults with us. Yes. And--

Hughes: Chiron was in this because of their money?

Urdea: In what?

Hughes: In the consortium--I mean agreed to this arrangement with Martin Marietta? What was Chiron going to get out of this?

Urdea: Yes, part of it was money, no question.

Hughes: Which you needed at that point.

Urdea: Sure. Yes. We always need money! [laughter]

Hughes: Sometimes more than others!

Urdea: The level of funding we need nowadays seems to be a little bit different than what it was back then.

Hughes: But at one point I heard a story, I think it was Steve Rosenberg that told me that he felt that, C.K. Chang--and I can't tell you--it was probably 1982--

Urdea: C.K. Chang.

Hughes: Chang. Maybe 1982--actually paid the salaries out of his pocket at one point because the funding was so bad.

Urdea: I think that's true. And C.K., I believe had a lot to do with the Martin Marietta connection. C.K.'s father--

Hughes: Talk a little bit about him.

Urdea: C.K. is an interesting character. If you can find him, he'd be interesting to talk to. C.K. acted as a purchasing agent at UC for quite a few years with Bill--

Hughes: UC Berkeley?

Urdea: UC San Francisco, with Bill. That's how Bill knows him. But CK is quite a wealthy fellow, and he gave at least three times his salary per year as donations to Chinatown for various functions. He didn't need that job, he wanted that job. He wanted to look at opportunities in selling scientific equipment and getting into this biotechnology area. So he was Chiron's first purchasing agent—

[Tape 1, Side B]

Urdea: C.K.'s father currently lives in the Century Plaza and I think he is on one of the entire floors. He was ambassador from Taiwan to the US for quite a few years, and as such has quite a few connections and can get in doors when others can't. He sits on the board of several different companies, at the time Pan Am was one of them.

His father, if I'm not mistaken, made the connection with Martin Marietta and got them interested in Chiron. So C.K. was an important person early on.

Hughes: How long was he with Chiron?

Urdea: He must have left--something like '86, '87, I would guess. Quite a long time at the beginning.

Hughes: Talk, if you don't mind, about what's happening to the physical space in these early years. Like what have you done after moving into the building here, and the first few labs?

Urdea: Well, the first few labs I mentioned are across the street in the other building. As a matter of fact, I called Pablo to suggest that the good place to set up the new company would be this building across the street. So they came over and saw it and finally agreed to do that.

So these were outfitted on one floor and I think we always underestimated the amount of space we were going to need--just every time, you get done and then it's time to reconstruct, or work it out, or start all over again. But a lot of moving around. This is my fourth building since I've been at Chiron. I started out across the street, been at the base center, came over here. There are some people now who have made at least seven moves that I know about. People in offices, that don't need laboratories, tend to be the first to go. So it's been a real hodgepodge. We didn't have all of this building in the beginning and then we ended up having all of it--kicked out other people who were here.

Hughes: And by "this building" you mean the main building?

Urdea: What is called the M building. I'm sorry, the Q building. There are three buildings here. This is the R building out here. The R building is the one on the southern most part of the parking lot. And then the building next to it that has the entrance with the glass structure, that is the Q building that was our original building. And then the one that sits perpendicular to both of those is the M building.

Hughes: Which is the Cetus building?

Urdea: No, Cetus wasn't in there. The Cetus building is on the other side of the street. And I don't know what the number is for that building. Must be the M building. So M building is the old Cetus building, Q building was the first Chiron building. Chiron then took over the Q building. Cetus then came into the R building, so then we moved into the M building. So Cetus was in fact on either side of us. We even had some doors where they could see right through. It was a glass door. We could see the Cetus office on one side and my lab was on the other side.

Hughes: Did you have any contact with them?

Urdea: We knew lots of people there, yes, we saw each other all the time.

Hughes: Was there any sense of competition?

Urdea: Plenty, yes. It was interesting. We were by and large working on different things, but there was a sense of competition in terms of technology: our ability to do DNA synthesis versus theirs, our ability to do expression versus theirs. These kinds of things were--a sense of competition. But we talked to each other a fair amount as well.

Hughes: You did--so there was no idea of "you keep your secrets and we'll keep ours?"

Urdea: Right, for instance, we would borrow chemicals from them and they from us. I'm out of dimethyl--dimethoxy tritylchloride and I go over to Kary Mullis across the street and say, "Can I borrow some?" and he'd say, "Yes, here you go." As a matter of fact he tells me I still owe him a hundred grams of dimethoxy tritylchloride which one day I'll pay him back. But that was good. That was a good relationship.

Hughes: And you've got to stop.

Urdea: Yes.

[End Session]

Interview #2: December 9, 1992
[Tape 2, Side A]

Urdea: So last time we were talking about the technology we acquired and developed ourselves, in house, to make synthetic genes. We had learned an awful lot through our connection to the Marv Caruthers' laboratory, but we also had made quite a few improvements ourselves in some of the support technologies and monitoring methods and coupling and all the other kinds of things. It must have been, oh, the very beginning of 1982 that we felt that we were ready to start making synthetic genes. The first one we made was the epidermal growth factor gene. There were four of us that were working on it: myself, Guy Mullenbach, Phil Barr, and Jim Merriweather. This was in the days when DNA was still made by hand. It was quite a grueling task. We'd make, usually, four fragments at a time. You'd do this in a fume hood, with syringes, and strange looking bottles, and compounds, and everything. We'd have color-coded vials for all the different bases that needed to be added on, flow charts, and you drank a lot of coffee [laughter] in order to keep yourself pumped up. It was grueling work, but when you got done making it we'd purify those fragments and then we'd combine them into the appropriate configuration to make the synthetic gene and then we started cloning it. We worked with some of the molecular biology people, in particular Doris Coit who worked for Pablo Valenzuela, to clone the first synthetic gene that we had made, and it worked beautifully.

Hughes: This was EGF?

Urdea: Epidermal growth factor gene. And then it just exploded. We next made two genes: insulin-like growth factor-1 and insulin-like growth factor-2. Both of which are still in the development as protein products here at Chiron. Those were our next two genes. Guy Mullienbach and I made IGF-1, and then Jim Merriweather and Phil Barr made IGF-2, and after that we just started making everything because we recognized that there was really very little limit to what we were going to be able to make. So I personally made human insulin gene, and I made four different derivatives at the same time. I cloned them all in one day. We'd become so proficient at it that it was really very easy to do. And that was involved with the Nordisk insulin work that I guess we started [looks at a list] somewhere on this list. It must have been--I actually don't see it, but I'm sure it's here.

Hughes: It is, I could find it. Well, the factor VIII contract with Nordisk was 1982. The insulin came a little after that.

Urdea: Yes, yes. And we did work with some of the people from Nordisk to teach them our DNA synthesis methodology.

So we would make these genes and clone these genes and we started making virtually everything there was. I mean, if it was in the literature, if we knew

about it, we were making it. We ended up with a lot more genes than we ended up with gene products, because it just became a bottleneck to try to express these things. And of course this is when the alpha-factor cloning system was being developed by Tony Brake. So these technologies of gene synthesis, and expression kind of merged at just the right time.

Hughes: And could all these genes be expressed and used?

Urdea: Most of them, you got some expression right away. Maximizing it was a significant task. But typically you got some product pretty quickly. So many tricks were developed after that as to how to orient these things, and the first sort of cloning that we were doing with alpha-factor involved a series of leader fragments on the front of these materials that would lead to unnatural products--so it would have extra amino acids on it. So a lot of what was going on was how to get around that problem. Tony Brake, and I think Phil, were probably the guys that managed to get around that with some alterations to the gene. But that was all done with synthetic DNA. We were working on several different ways to do it simultaneously because we could so facilely change these things.

Hughes: Do I conclude, from what you said before, that in a sense the technology was outpacing the application? I mean you could do these things without necessarily knowing what purpose they serve.

Urdea: Quite frankly, I think that was one of the big problems with a lot of biotechnology companies early on. Firstly, we knew we could make almost anything, but we really didn't realize what we were going to do with it. I think, obviously, Rutter knew a lot more of what he wanted to do with it than we did, but those guys, like myself, back in a lab, I know we were very naive about what it was going to take to put this out on the market. We just knew, hey, we can make these things, let's go, let's go! [laughter] So we'd keep lining the shelves with new vials of genes.

Some companies even sprung up and said, "We'll make any gene you want." One company Creative Biomolecules was started by the guy who set up DNA synthesis at Genentech, Roberto Crea. They tried to do that; they tried to just market genes. It didn't work out because you have to tailor them for everybody's specific application. And people, once you get a couple of expression successes in some of these things you say, "Well, I can express everything, anything." And of course that ended up being true. You could make minute quantities, but making enough that was economical and manufacturing sort of levels--that was a whole other story.

Hughes: When did those manufacturing capabilities come in, and were they tailored--I mean did each manufacturing scale up, if that's the right terminology, have to be tailored to the specific product, or was there some generalizable scheme that could be used?

Urdea: Some people may not agree with me, but I would say that it was not generalizable at all. We made EGF and alpha-factor and got a remarkable amount of material. And I think everybody thought, "We got it! This is the holy grail of expression systems and we're going to be able to make anything at any level we want!" Well, that didn't hold up. To make some of the other materials a lot of other tricks were used: SOD fusions, which ended up being a very good one that Patty Olson, I think, was the one who originally suggested and developed it. Lots and lots of tricks depending on which particular material needed to be made.

Hughes: Which were devised with a scientific rationale, or almost by serendipity?

Urdea: [Laughs] All of them had scientific rationale. I would say it was serendipity as to which ones worked. I mean, basically we tried a lot of different things. "How about this promoter, how about that one. How about this leader sequence, how about that one. How about this fusion product, how about that one. How about this orientation; how about this length of promoter; how about this codon usage; how about this kind of processing sight." Many, many different things. "How about yeast versus bacteria versus insect cells versus human cells."

Hughes: Did you try all those?

Urdea: Sure. Depends on what the project was. In some cases you just tried everything you could think of, because it was a lot easier than any other approach.

Hughes: Now, if you'd still been at UCSF, would you have proceeded in this general fashion?

Urdea: No way! We couldn't have afforded to. The big difference between industry and academics is teams. You cannot do it--there are some academic organizations that work like that, but by and large you just can't put a team effort together like that. You don't have centralized technologies that you can tie into, and you just don't have, probably, enough money, to pursue all these things simultaneously. So, in many cases, these things were only things that could have been done in industry. I think there are still so many projects like that, that you just never see done in academics. They can't do it. So it was a very different process in industry than I can recall in academics. And you tried a lot of things.

Hughes: I'm thinking of the introduction of the mammalian cell lines which are, if I remember right, was about 1983, you're not right at the beginning. Did that mean that people then had to learn it or did Chiron go out and try to attract those people who already knew how to work with mammalian cells?

Urdea: You don't really have time to come up the learning curve on these things. If you know there's somebody out there that already knows it you've got two choices: go out and hire them, or get them to collaborate with you. And there are lots of ways to do that: they can be a consultant, or you can send people to their lab to train. But the best way is to get people who already know how to do it--proven track record in that area. And we have done that wherever we could ever since the beginning. I think that Bill has always been particularly good at finding those kinds of people. But even when he had his academic lab, how should I say, even when I was in his academic lab, that's what I think he did really well. He'd find people to collaborate with and send maybe me--I went off to a lab to learn DNA synthesis when I first got to Bill's lab--or somebody would go off to Fred Sanger's lab and learn how to do DNA sequencing. And those technologies would get set up in his lab, instead of just trying to read the literature and work it out. We don't have time for that, and you won't be able to compete.

Hughes: And the whole premise of that department was set up on that idea of individual projects, but a strong collaborative emphasis?

Urdea: Yes, and that's the way Chiron operates. Chiron operates very much on a large scale the way Bill's lab used to operate. And Bill was really good about having teams in his organization. But the collaboration thing, you know, we can't do everything. Collaborate with somebody else who's already doing it and get them to do the part you can't do. It'll strengthen both of you.

Hughes: So that is a stronger characteristic of Chiron than other biotech firms?

Urdea: I think so. It's something that people call NIH, Not Invented Here syndrome. You can't have that. That has been the demise of many a company who will say, "Hey, I can do it better than them." And then they spend a lot of time getting up to the same place they saw them at and it's too late, those guys are already way beyond you. So, you then have to leap-frog it or forget it. So collaborations make that much better. NIH syndrome.

Hughes: Do you want to talk next about the diagnostic emphasis, and when did that come in and why? Because the first emphasis, correct me, but of course it was the vaccine, the hepatitis B vaccine, and then there was sort of some projects which, I gather, were just mainly to bring money into the operation.

Urdea: Yes, of course.

Hughes: And then is it the diagnostic phase which was the next major emphasis that comes along?

Urdea: I would say that the diagnostic phase was always considered but never really pushed until AIDS. And, of course, Chiron was right in the fray of the whole thing from the beginning, in the cloning of AIDS virus. I think what was

obvious to everyone immediately was, my god, you need to screen for this in a blood bank.

From even before Chiron was started, I know that Bill Rutter had been talking long and hard with Lacy Overby, who was at the time associated with Abbott, and many people would say the father of hepatitis B diagnostics. Lacy came to Chiron to join as the head of diagnostics. I think AIDS made that all seem like the right thing to do.

I think there was another thought too, and it had to do with the growing sophistication of the people involved in this, and that these therapeutic products are going to be fairly long term to get to the market. Let's see, we got these antigens for these organisms and what else can we do with them? Clearly diagnostics is such a thing. And it was, it is, a big market, there was a big need for it, and it was something that we felt we could do with having Lacy here and hiring a few key people to do that, that made all the sense in the world. Now it's a matter of how to configure those things. What kind of assay formats are we going to blood banks or diagnostics with? But I think it was viewed very early on as an opportunity to make short-term money to fund the therapeutic effort. I still think that's the way it's thought of here. And it makes a lot of sense. Abbott did it very well.

Hughes: Who would be making decisions like that?

Urdea: In those days probably mostly Bill and Ed--along with the board of directors which has changed in composition. But I would say probably Bill and Ed.

Hughes: And how big of a role do you suppose the board of directors had? I mean, were they more than a rubber stamp?

Urdea: In my opinion, no. [laughter] At least, let's put it this way: if they had a large input, it wasn't obvious to a lot of those who were involved.

Hughes: Now, was that okay with you, or did it make you nervous that decisions were being made on the basis of two minds, essentially?

Urdea: I think a lot of us have always had a lot of faith in those two minds. So, you know, I think that they, all of us, have made a lot of bad decisions over the years. But as soon as we recognize that that's the case, we try to correct it. And I think as long as you are willing to do that and you get the best information you can at all times and you just keep going forward, that's fine. I think that those guys are so objective, or at least try to be, that they correctly evaluate their decisions and are willing to go change it. So I feel really comfortable with the way they do things.

Hughes: It's still pretty much that way, is it not?

Urdea: Absolutely yes. Absolutely yes. More and more of us are involved in decision making. We have this strategy committee here that involves several key people. And I think that's become a very good organization. They still call the final shots, no question, but--.

Hughes: Who's on the strategy committee?

Urdea: Well--it's quite a few people.

Hughes: Is it the choice of the higher-ups, or is it a formula, such as division heads? I mean, is there automatic membership?

Urdea: No, it isn't. It's composed of mostly vice presidents, but not all vice presidents. So, you'll see the R&D heads and business unit heads, head of legal, finance, those kinds. So Denis Winger, Bill Green, R&D people, like myself and Pablo, Walter Moos, Dino Dina. Business unit heads, Bill Gerber, Jacques Martin, Jim Rurka, Bill Link, and a few others. So that's a good mechanism.

Hughes: Do you remember when that committee originated?

Urdea: Well, that committee of that composition, only within the last year.

Hughes: Oh really, so really late in the game. And there was nothing comparable before that?

Urdea: Yes, there was an executive committee, and I quite frankly don't know what the make up was just before they changed to this. So who the key people have been has fluctuated except for Bill, Ed, Pablo. Those guys have always been around.

Hughes: Say something, because I really don't know, how Chiron compares in structure to other biotech firms. But it seem, from what you're saying, that it's been very much a process of evolution, you know starting with a group of people who had an association and had some ideas about how they want to start. And just, sort of as time goes on, functions are added--

Urdea: --and subtracted, and changed. I joke about this all the time around here--every time you think you know where things are and where they're going on, I guarantee it'll change--like the next day. And I swear to you that's the way it is. I mean, about a year and two months ago I finally thought for the first time that I really knew where things were going and I could see out a couple of years.

Hughes: You mean what the avenues of interest would be--

Urdea: I knew what the structure was going to be. Greg Lawless was president, we were going and doing this kind of diagnostic product, I knew what our budget was going to be for a couple of years, and then we merged with Cetus, Greg left, everything changed, just like overnight. [laughter] So--

Hughes: So much for that stability.

Urdea: That's right, that's right. [laughter]

Hughes: Well, is Chiron more--it's pejorative to say instable, but let's put "flexible" as an adjective.

Urdea: I think that's a good choice of words, quite frankly, because I don't really consider it to be unstable. Some people probably view it that way, and they get uncomfortable and leave. It's not unstable. It's very flexible. It really is like an evolving species.

Hughes: And you're speaking relatively too, I mean in comparison to other companies.

Urdea: I might be wrong, and that's because I'm such an insider here. But when I talk to my friends who work at other companies, I don't see it as quite as rapid and complete a change as I've seen here.

Hughes: Now, how much of this do you think is a function of the three people at the top and their personalities?

Urdea: I don't know. I'm sure a fair amount has to do with that. But it also has to do just with taking advantage of current opportunities. You may need to do things differently than before in order to do that. We're always looking at new ways to do things. And I think it's also a matter of constantly being willing to change and finding it necessary to challenge the dogma of the way things are done. A company like ours, we were always good technically, we still are, but we have to be much more than that. We also have to figure out what's the fastest and easiest way to get products to the market. When we look at the paradigm of another company, and the way they did it, they have a very special way in which they go from research, to development, to process development, to manufacturing, to sales. We have to think of ways to make it go more quickly than that. Just say, do we really need to do it that way, can we do it more cheaply, can we do it in less time? We have to be as creative in that process as we have been in the science that got us to what we needed to be doing. We're constantly looking at that.

Hughes: Do you think it's ever been a liability to not have a stable, one business figure at the top? I know you've had some, but they seem to have come and gone at a rather rapid rate.

Urdea: [laughter] Yes.

Hughes: What sort of impact has that had?

Urdea: I think--not that much. And that's because the reason most of those people probably were uncomfortable, I don't know, is because their influence wasn't as great as they might like it to be. I think the other thing is that it's only been relatively recently that Chiron has been making money, and that you really need to focus on the business side of things.

And I think now we've got some very good people on our board. Our board is no longer a rubber stamp by any stretch of the imagination. In fact, it is remarkably involved and I think it's great. Especially people like Jack Schuler who take such an active part, Henry Schramack who takes such an active part, and some of these other people. I think it's just a wonderful transition for us at the right time. That's what we need now.

Hughes: And when did that new board come in?

Urdea: Well, it's changed a bit over the last year and a half--a whole lot.

Hughes: Well, the Cetus merger, I'm sure, changed things.

Go back, if it's something you want to address, to the AIDS question, because so far nobody's talked about that and I'd like to start back with the Jay Levy connection and where that originated.

[Pause] Is that something you want to talk about?

Urdea: Sure, but I probably can't give you as much good detail as Dino would on this. Dino's probably the best person to talk about that. But Dino--I don't know who made the initial connection with Jay, I don't know if it was Rutter, or Dino, or both, or what--but that was very important for us. It appeared as though Jay probably had an isolate that was the virus, nobody knew what it was yet, or how it grew, or all the other things. They knew they could grow it, but cloning the material was tough.

And so this fellow Paul Luciw and then Dino worked very hard to clone that material in just record time and then started sequencing it, and Ray Sanchez-Pescador, who's in my group now, and several other people, worked day and night like crazy to get this thing done. That really set the stage for where to go. We started using all these systems, synthetic genes, cloning vectors, and all the other things that we had developed for the growth factors, and it was just a perfect opportunity for Chiron--just the right thing to do at the right time. And because of that technology we had a place in and a connection to the Levy lab. We were just flying.

I think people, when they look back even five years from now, look at what happened in the patent situation, are going to be really surprised at who did

what at what time. And I think that that's already starting to come about with the allowance of some of the patents Chiron currently has.

But the obvious first things to do were in diagnostics and trying to find the right parts of the virus that would give you response with all the different known samples from people who were infected. That ended up being a big task. What parts do you need? Do you have just the GAG-protein, or just the N-protein, or just the whatever? I think we learned a lot about how to do such things and how not to do such things. It was a real learning experience. I think we look back at it and say we made a lot of mistakes, and we wish we had done it differently. And when HCV came we knew what to do [laughter]. There aren't too many companies that have had the chance to do it twice, and correct the mistake the second time, but, you know, we got it done.

Hughes: Who were the competitors in the AIDS diagnostic business?

Urdea: Clearly it was Abbott. There were five companies to which the virus isolate had been given after NIH had it.

Hughes: And that was a NIH decision?

Urdea: I don't know exactly who made the decision. I think it was the FDA involved as well. There was a lot of concern about whether or not if one company had it, let us say, that the product would be available in high enough quality to ensure that the blood supply would be clean. So the decision was made to look at the various companies that could produce the blood screening product and give them all equal opportunity.

Hughes: Now, was this decision made after you had sequenced the gene? [Pause] I guess what I'm really asking is why Chiron? Or why any of them? Because presumably everybody that had been working on the problem was not a player.

Urdea: Well, there was a lot of debate at the time as to who had it first, you know the French versus the Americans as they would say, but it was really also Chiron versus the Gallo group. A lot of people don't remember that. But it was that one NIH isolate that was shared. So the products on the market were antibodies against the whole virus, not against parts of the virus made by recombinant DNA.

Hughes: And Chiron was in on that first--

Urdea: No, not the--no, we weren't. In fact, we were not privy to that isolate.

Hughes: Because you've always used (_____) the San Francisco, I presume--

Urdea: Yes, yes, that's right.

Hughes: Has that had advantages in that it hasn't gotten caught up in all the controversy between the French and Gallo?

Urdea: Yes, perhaps, but I think the question in their mind would be did they have any rights to it at all--why are they wasting their time going forward with this? But I think that--

[Tape 2, Side B]

Hughes: At R & D some companies working with multiple isolates?

Urdea: All companies that know what they're doing are working with multiple isolates. So, as a matter of fact, I think it's something I think we understand much better about HCV than we do for HIV.

Hughes: Well why don't you tell that story, HCV, if you feel you've said enough about AIDS?

Urdea: In my opinion we did do a good job in the diagnostic area for AIDS. If we had known more and done certain things we probably could have done extremely well in AIDS diagnosis very early on.

Hughes: Can you give me an idea of what some of those wrong avenues were?

Urdea: It actually was a controversial area that I argued vigorously for, but nobody listened to me. [laughter] But fortunately Ed Penhoet remembers that I said this.

Hughes: [Laughing] And it's now on tape.

Urdea: I thought we should do what they call "shotgun cloning," which means that as opposed to assuming that we knew which part of the viruses are likely to react to an antibody, we should have pretended that we didn't know and then cloned little pieces and looked for which pieces reacted with sera. We didn't do that at Chiron. Other companies did.

Hughes: Why not?

Urdea: Because everyone thought they knew from the structure of the virus what the right area would be, just *a priori*. So that was not a good way to go. And it ended up that a big surprise came about, which was that a region called P31, a polymerase enzyme, was reactant with the antibodies, and there were individuals who had a lot of this antibody. And you probably needed it in the test. There were some people who *were only* P31 positive. So other companies saw that before we did. That was not too pleasing. So that's one of the sorts of things, but mostly it was a matter of what kind of configuration

of assay we should work on, and I think we didn't work on the right configuration of assay at first.

We worked with another company that had an instrument we thought we were going to be able to put the test on this. In fact I did a lot of work on this. We were going to run assays on a bead and detect it with fluorescence and there were a lot of problems, technical problems, that we just could not overcome.

Hughes: What was the company?

Urdea: It was called Pandex. They had a machine called the Screen Machine. And it sounded great, but we probably shouldn't have tried to use new technology for the assay with new antigens at the same time. My personal wish is that we had picked a very common format and just stuck it in that, and focused on that.

Hughes: There are too many variables.

Urdea: Too many variables, yes. And just realizing what a large effort it was going to be to develop these things, manufacture these things, get regulatory approval for these things, and put it on the market--I don't think we appreciated the level of effort that would require.

Hughes: And at that point, I forget what year we're talking about, maybe 1986?

Urdea: Yes, about that.

Hughes: Had the FDA begun to let up at all in its approval process? In fact, I don't even know if they did for the test, I'm thinking more of the drugs, aren't I?

Urdea: As a matter of fact, the polyclonal antibody assays got out rather quickly by necessity. But it took a long time, and I don't even know how long, before any recombinant-based AIDS diagnostic was approved--years, years. And it was a lot of these concerns about changes in isolates and those kinds of issues.

So for HCV--I guess that we can switch now.

Hughes: [Laughter] Yes, get on to what you really want to talk about.

Urdea: You know, that was record time. I was not involved in the immuno assay or the cloning of that original material at all. I've been involved in the DNA probe aspects of it. But, how to approach the cloning process, how to approach looking for the right antigens, how to configure assays, how to develop an EIA, the ELIZA format--very smart, simplest possible format with complex antigens. Great way to go. We beat Abbott, you know. That's saying something.

So from the immuno assay side I think that the lessons we learned were put in place. But for me, most of my time at Chiron has been spent on DNA probe technology. HCV was the first major opportunity, and we now have embarked on the market for HCV detection using probes. It's only been on the market since October 1st. So we're out there pedaling it now. But we developed a whole set of technologies over several years. I started in 1983 working on it, and our first product was October of this year. If somebody told me it was going to take that long I don't think I would have believed it.

I won't bother talking about all the different technologies we've developed, but for HCV the thing that I was really worried about right from the beginning was this whole issue of strain variation. So we spent a lot of time looking at isolates from all around the world, and sequencing different portions of them to understand how the variation occurred, and what prevalence it is, and then finally in designing the oligonucleotide fragments that we would use to react with the organism, so that we could say, "Look, I don't care where this sample comes from, and we know what the genetic variation is, but our probes will react with it. In fact, here are some examples where we have proven it." And we can say that; we've done that. And that's, of course, also in anticipation of things that the FDA is going to ask us.

So we've seen variations from samples throughout the world: Japan versus the United States, all over Europe, South Africa, Argentina, and Australia. We've looked at multiple isolates from those different places and asked, "How does the sequence change?" Interestingly, you can find the same sort of variants all over the world--except so far in Africa, we've found a unique form that we haven't found anywhere else. You have to think about that and pursue it way ahead of time or you'll never catch up. In other words, if you have an immuno assay on the market and you got the wrong antigen in it, or you got an antigen that's limited to a small number of strains, and the FDA says, "Well, does your test react with the other strains," it's going to be a long time before you can come back with an example of testing other strains.

Hughes: Does this mean that there was quite a large group working simultaneously on different strains? How did that work?

Urdea: Looking at sequences?

Hughes: Yes.

Urdea: Initially, several different people here were looking at that but finally just people here in my group, three people who were working on it, who got samples from all over the place. But three people could handle it pretty well. We'd sequence sixty or seventy isolates and different parts of all of those and just compare them all by computer. We published it, finally, just last year.

Hughes: Why so late?

Urdea: Publishing it?

Hughes: Yes.

Urdea: Quite frankly, publishing it wasn't that much of a priority. Why should we want to let everybody else know? But the issue has come up so many times, and we wanted to make sure people recognize that we know more about it than anybody else and that we took all of this stuff into consideration in developing our tests. We wanted to be able to say, "Look, we know what the variations are. Here, it's in the literature. And, this test works with the variants." It gives people a lot of confidence in the use of our test.

Hughes: Say something about the wider significance of this test. And I'm thinking both in the obvious area of diagnosis, but I'm also thinking of what it meant to Chiron, both in terms of money, and in terms of prestige. And morale building.

Urdea: Yes. Well, if it weren't for HCV I don't really know where Chiron would be today. I don't want to think about it. But this was a major discovery. Mike Houghton is probably being considered for a Nobel Prize. This is the first thing of this size that has been done in a company, certainly at Chiron, and it meant everything. The company so rallied around that, so much of the company was shifted to working on the diagnostic and working on vaccines now, working on every aspect of it. We're maximizing this thing to the hilt. It's amazing how much can be done with one virus. I don't know what to liken it to, but it's like using one of the Brahma bulls, as the Indians do, for everything. You make clothes out of, you use the dung for the fire, if it dies you eat it. This is what has happened to HCV. And the diagnostics group was the beginning, but I think that vaccines and therapeutics for it will ultimately be even bigger for Chiron--much bigger.

Hughes: And where are those in development?

Urdea: Further behind. Vaccine--I really can't really comment on where that is right now. Lots of things are being tried. One of the problems is that you can't grow this virus all that easily. There aren't the sort of in vitro systems to test these therapeutic agents. So today, at least, it's a much more difficult thing to test than HIV. But there're lots of strategies. One would be the use of these vaccines. Another would be nucleic acid based therapies, gene therapy, or antisense--antisense being oligonucleotide or oligonucleotide derivative that can be directed against the virus to deactivate it. That's a whole new area that's suddenly flourishing. Got a lot of companies devoted to it. Chiron has recently gotten into this area.

Hughes: And again, how? By acquiring people who were--

Urdea: Well, in this case we have a deal with a recently started company called Lynx Therapeutics. They sprung out of Applied Biosystems, out on the Peninsula. We own a part of them and we're doing some work with them on HCV, HBV, HIV, and trying again to collaborate. They know how to make certain types of derivatives, they know how to manufacture them, they can do it on large scale, and we know how to test them. It's a very good collaboration, and it makes a lot of sense for both of us.

Diagnostics is a tool to develop these therapeutics. I think that's something else that I didn't mention. But as time goes on I think we realize that more and more. If you don't have a way to measure the amount virus there is, it's very difficult to develop therapeutics. You want to be able to, with a therapeutic vaccine or a therapeutic drug, introduce the drug to an individual and say, "The virus level went down." There aren't any convenient ways to do that today. That's why we developed these tests: the HIV test, HCV test, the HBV. You want to look at the efficacy of therapy for HCV. You need to be able to measure the amount of virus that's present in blood, let's say, or in tissue samples. So I think that this test that we've developed is going to help us and others to develop drugs to treat these diseases.

So, I would say, Chiron hasn't even come close to fully leveraging HCV. I think the thing we have to fear, quite frankly, is there being another equivalent of HCV out there. What I mean by that is, the next AIDS, the next HCV, that gives another company the kind of edge we have today in negotiations.

Hughes: Is there anything that you care to say about the partnership, is it, with other diagnostics?

Urdea: I can't tell you very much because I frankly haven't been very much involved in it. Probes has always been very separate from it.

Hughes: But there is a connection with a Japanese firm?

Urdea: Yes, Daiichi Pure Chemicals. That I can tell you about. We, in this probe area, decided some years ago that we would like to try and find a way to get some external money to help out. Quite frankly, Chiron has always been willing to take technical risks, but less so economic risks, and so find somebody to share that risk with you. So that was the intent with looking for another partner, and the notion was to try to limit it to some market segment so that Chiron could set up a fully integrated business in probes, and sell it wherever else we didn't have sold off, essentially. So Daiichi ended up being the company. We looked for a while for potential partners in Japan and elsewhere. In fact, in 1988 I spent--I remember I counted--I gave seventy-seven seminars to thirty companies on this technology that we were developing, and what its potential was.

Hughes: Was the focus on Japan?

Urdea: About half of them were in Japan.

Hughes: Why was that?

Urdea: Well, a couple of reasons. One was because of the potential market segmentation. You can say, "You get the rights for Japan, and maybe some other part of Asia, we get the rest of the world." And since so many Japanese companies are focused only on the Japanese market, that's a little easier to do. The second reason is long-range focus. This was not something they were going to have in one year, or that we were worried to just distribute today.

Hughes: And the Japanese tend to understand that?

Urdea: The Japanese tend to understand that and they think that way. Although I think that's changing within big companies.

Hughes: When you say these relative things, are you thinking of the American scene?

Urdea: I was just going to say, European companies were kind of in between, and the worst case was American companies. It was almost a waste of time to talk to them.

Hughes: Because of the long time scale, basically?

Urdea: Yes, relative long time scale, which is not worth it to them. The attitude was more like, "Come back when you're done. Not worth the risk." We'd say, "We'll come back when it's done. Of course it's going to be a lot more expensive." But Japanese companies ended up being the most willing to get involved. In fact, it wasn't a matter of finding somebody; it was a matter of paring it down to a few that made the most sense to us. So Daiichi was the one, and we've had this relationship with Daiichi now since officially November of 1989. It has been quite an interesting experience, dealing with the cultural issues and dealing with the technical issues.

Hughes: Can you sketch how the breakdown of labor does occur?

Urdea: It's mostly our labor. [laughs] That's changing now because we're getting regulatory approval for these things, but up through about the middle of last year there wasn't a lot of involvement from Daiichi personnel, except to monitor what we were doing and to determine whether or not we'd achieved the goals that we said we would. And for quite some time we were literally right on schedule. We're not far off of where we wanted to be even today.

Today, the issue is doing clinical trials on these tests, HCV and HBV tests, in Japan--that's happening right now. And then to submit the results to the Koseishio, the Japanese equivalent of FDA, and try to get approval for them. And there is a lot of involvement, and here is where the cultural issues, the

cultural differences between Japan and the United States are just coming into focus. I just returned from Japan on Saturday and we spent a lot of time last week talking about these issues.

Hughes: I'd be interested in hearing what you--

Urdea: I'll give you some examples. The way you run clinical trials--in the United States, the company can take a lot of control over this thing. What we would do if we want somebody to learn how to use the assay, we'll bring them in here for a couple of days to train. In fact most of the people that we train stay here for five days. I mean, we're on a very rigid training schedule.

Hughes: Now who are these people?

Urdea: This would be people from like at Mayo clinic, or at UCSF, maybe at--a variety of places--NIH. Each of those are places that have been here--University of Washington. And they'll be clinical laboratories, by and large, people that want the results of the test, and do testing. This will be, let's say, Hepatitis C testing. So they send representatives from their labs, they work here. And then they go back to their laboratories. We send people into their laboratories to stay with them for a few days, set it up there, make sure that they can run it. By the time they've got it done, they've run proficiency panels--they've run certain samples that we've given them that we know the results for. And we say, "We're not going to set it up in your lab until you pass that proficiency panel because we won't be able to trust the results." And they say, "Okay."

Hughes: Now is this standard procedure to do this?

Urdea: Standard procedure. Well, some companies might not do it this way. But in a new technology like this, where you want to be absolutely certain that they're going to be able to do it, this is standard procedure. So, you get it there, and then for several weeks after that we in fact have them fax to us the results of their tests, and we evaluate it for them. So that's how far we go.

Hughes: Intensive.

Urdea: Very intensive. Very intensive. Meetings, telephone calls, and then let's say they want to publish. I just went through this today, I've got two or three abstracts up there from people who want to present results at meetings. They always send us the abstract first for review, and then we say, "Okay," and they send it off.

Hughes: Now is that a stipulation?

Urdea: We don't have to have anything in writing. That's just common courtesy in the United States and Europe.

Now let's go to Japan, same sort of situation, what happens? We suggested that they do this in Japan, and they were like, "Oh my God, we'll never get to do this." It's a matter of relative, I guess, attitude, for one. In the United States the people in the field tend to have a pretty fair amount of respect for the people in the industry doing these things, as scientists. In Japan, the academic people, clinical people, look on these industry people like the scum of the earth. And the industry people tell us that too, "Look they don't think very much of us." Not because they're not good, they are, but just because that's the general posturing. So, we want them to come and learn the assay in Daiichi's laboratory--no way. No way! Nobody would do it.

So we had to go to the customers laboratories and we get two days. In fact, most of the afternoon of one day and the morning of the next day, which is just enough time to run the assay and look at one set of results and then they say, "Goodbye, I don't want to talk to you anymore. Now we're going to just run the assay. And when we get around to it we'll send you the results." Which they've done. Sometimes it works, sometimes it doesn't. And when it doesn't they may not ask the right questions, and they may not even want the help. It's very difficult, it's out of your hands. We ask Daiichi for the results, they say, "Well, we're trying to ask them for it but I'm not sure we can get the results."

Hughes: It's probably an issue of face as well.

Urdea: Yes there is, definitely. And then we say, "Well, we have some meetings coming up, are they going to be submitting abstracts to the meetings?" "Yes." "Well, we'd like to get those abstracts for review before the meeting." "No way, we can't ask them for that." "Wouldn't you normally review that?" "No. The doctors will do what they want. We have no control over that." So it's completely different. And from our standpoint it's very uncomfortable because we can't control it.

Hughes: It's your test being used in a way that you may not approve of.

Urdea: As a matter of fact, it's clear to us that they're not even following necessarily the instructions that we give them, or the sets of parameters that we've given them to determine whether the test is working or not--the so called "product insert."

Hughes: Now, why? Is that again just that they know how to do it?

Urdea: That's right, they say, "I know which samples are positive and negative and I will determine what the cutoff value is for the assay," for instance. I had this discussion with them during a meeting several months ago. They told me that during their clinical trials they wanted to set the cut-off for the assay. I said, "Excuse me, but Chiron already set the cut-off for the assay. Please simply

verify that the cut-off is correct." "Oh, well," all kinds of discussions and they finally agreed that they would simply verify that the cut-off is correct.

Hughes: It was not a given. [laughs]

Urdea: It was not a given. And there are very few givens. So this reflects some of the major cultural differences and attitudes of people in Japan versus virtually everywhere else I go.

Hughes: And it's less of a problem in Europe?

Urdea: Not a problem at all in Europe. In Europe they're very much like the U.S. and they would want to have this kind of training and level of support.

Hughes: Well, we're beginning to run out of time. Do you want to talk about the merger with Cetus? Actually, let me ask you an open ended question. What would you like to talk about? [laughter]

Urdea: I don't know--.

Hughes: The Cetus thing is very recent. Maybe you feel it's too recent. But obviously that had--

Urdea: It might be [pause and rustling of papers] I'm trying to see--.

Hughes: Is there more of the science, since that's what you are, I mean you're a scientist, that you might have a viewpoint that others don't. An insider's view that we haven't brought up.

Urdea: I might tell you one little story that you might find amusing, I don't know. This whole DNA probe are. You've heard of PCR?

Hughes: Oh yes.

Urdea: Yes? PCR was invented by Kary Mullis. Well, Kary and I used to see each other fairly often because when Chiron first started, at Bill Rutter's lab, we were across the street in the same building as Cetus, and Kary was downstairs from me in that building. In fact, our labs were one on top of the other. We used to borrow reagents from each other, and we'd work on DNA synthesis sort of problems together. We had something called the Bay Area Peptide Group, Kary is the one who set it up, but it involved not only peptide chemistry but also DNA synthesis chemistry. In 1983, if I recall, we had one of these meetings and a fellow named Helmut Blocker was here from Germany to talk about some chemistry. After that meeting, we were just talking about what we were working on and Kary, who has never able to keep a secret, told me about this method he was working on. He drew it on the board for me, and showed me, you know, it does this and this, and talked

about the reactions. He hadn't got it to work yet, to my knowledge, I'm not sure, but he told me about it. And I looked at it and I said, "That will never work." [laughter] It was PCR, of course. He never lets me forget this, every time I see him.

Hughes: Now, why did you think that?

Urdea: I thought that the primers he was going to use, for the PCR, would bind non-specifically to so much of the other material that would be present in the sample, that he'd never get the specificity he needed. And that is a problem with it, but you can overcome it. So that was my concern.

Hughes: Which he didn't know at that point either. I mean he didn't know whether he could overcome it.

Urdea: Sure, not at all. But, you know, I rarely say, "That will never work," anymore. [laughs]

Hughes: But apparently, you were not the only one to tell him that it was a worthless idea.

Urdea: I didn't think it was a worthless idea, I thought if it worked this would be great.

Hughes: "A worthless technique" may be better.

Urdea: I didn't think it would work to do it the way he was thinking. And I guess I was also just so focused on the methods that I was working on.

In fact we are today in very strong competition--the technology I developed, and the technology he develops. The PCR--we'll never replace PCR applications in a research lab and techniques that we've developed aren't good for that. But something that we developed called b-DNA amplification--

Hughes: b-DNA?

Urdea: Branched-DNA, b-DNA. PCR is what they call a target amplification method, and b-DNA is a signal amplification method. We look at the amount of RNA or DNA at its physiological level in the sample. So the technique that we developed can detect a few thousand molecules, like three thousand molecules, directly. Whereas in PCR you make more of the RNA or DNA, and then detect it using conventional methods. So, I personally think that b-DNA will more useful in the clinical laboratory, and that's where we're focusing. The other thing it does is it quantitates, it tells you how much virus there is. That gets back to the whole issue of monitoring therapy. You don't want to just know if it's there, we want to know how much of it's there. But anyhow, I told Kary that PCR wouldn't work.

[Tape 3, Side A]

Hughes: I have been puzzling over when science becomes technology, which may be an impossible question to answer, but it seems to me--

Urdea: I think it's a good question.

Hughes: --in biotechnology, whatever the basic science is, molecular biology, on the other end. It seems even a tighter connection. First of all, is that true? And is this something you'd like to talk about?

Urdea: As a matter of fact, a friend of mine, Mark Zoller-- he used to be at Cold Spring Harbor and I think he's still at Genentech now-- well, I remember a conversation he and I had several years ago about the difference between a scientist and a technologist. He and I are much more technologists that scientists, and I think it really gets down to: do you answer fundamental biological questions, or do you develop tools to do that? And I like to develop the tools. I jokingly say, "I'm much more interested in enslaving mother nature than in understanding her."

Hughes: At least you're frank about it. [laughter]

Urdea: I really like thinking about how to put things together, to develop tools to sequence DNA, or to detect DNA, or to synthesize DNA, or whatever. I think that's much more technology. And that then is an enabling capability for someone who wants to answer specific biological questions, scientific questions, like, "Why does this organism work?" So I think biotechnology is a much better description of what most of us do in this company than bioscience.

Hughes: But, can you say that Chiron does exclusively biotechnology?

Urdea: Absolutely not. As a matter of fact, in some cases, until we understand how certain things work, there's no way in the world that we can justify building the tools or anything else.

I think vaccine development, for instance, and some of the therapeutic developments, require a fundamental understanding of the systems. The immune system, for instance, or oncology--why does cancer happen? Until you understand that, you can't develop anything. You need a few tools to figure that out, but then you're not going to go any place until you discover some new molecules. And to discover them you have to search for them, you've got to understand what the process is that they're involved in.

We don't do as much of that at Chiron as we used to, and I think it's something that we all struggle with. We have to, as more and more companies like our own become mature, we're going to have to tie into

universities. And quite frankly, that's the smarter place to have that thing done, and I'd like to see more and more money flow back to that to do that. The obvious conflict is that then we might ask for that research to be applied to what we're doing.

Hughes: And that has to be worked out.

Urdea: I think it's more appropriate for us to do the technology and them to do the science.

Hughes: Well certainly UCSF seems to be moving in that direction.

Urdea: Yes, yes.

Hughes: And just their general funding situation in science, it certainly has to come from somewhere and it's not going to come in enough quantities from--

Urdea: I think there's a happy compromise in the whole thing because I think you can say, "This is a cancer laboratory and they're looking at breast cancer, and I'm not going to tell them what to do. But I want to make sure that they learn as much as they can about breast cancer, and I'm going to check on this and I may have some suggestions here and there. But by and large do what you think is the best thing to do. And we're going to look how to apply that when we can."

Hughes: Do you think it can really be kept that discrete though?

Urdea: No. It's going to be hard. It's going to be really hard.

Hughes: Because of course that's the nay-sayers who have been with us since the early seventies, that was one of their big prize. You know, the basic impetus of science--the free inquiry, the free exchange of information, the randomness of it, follow your lead and go with it wherever it might go--is certainly not the way it can happen in industry. And there was the worry, when the tie between what was happening in academia and in industry became tighter, through biotechnology amongst other fields, that there would be this hampering of scientific inquiry.

Urdea: Yes, and I suspect that a lot of people would say that they don't have enough money to do the science they're interested in, and that's probably true. Until the U.S. economy gets to a level that it used to be at, but isn't anymore, I don't see how that's practical. Maybe you have to do a little of both. Maybe there's some compromise say, "Do half of this stuff for us, and do the other half whatever you want." I don't know what the compromise is, but hopefully we can find it. Because I think we can't forget the fact that so many discoveries have been serendipity, and that plays a much bigger role than we give credit to. We just can't let that stop.

How to regulate the whole thing, I don't know. Sometimes I think we should just dissolve the NIH, the NSF, everything, and we should have enormous prizes for certain things. For instance: let's have a five billion dollar prize for the cure of AIDS. Stop all funding and just see what happens. I bet you'd get a lot of private sector money devoted to getting that prize. We'll give them a two billion dollar second prize, you know.

Hughes: Runner up.

Urdea: Yes.

Hughes: It's an interesting idea. [laughter]

[End of interview]