Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in Bioscience and Biotechnology Studies

KEIICHI ITAKURA
DNA SYNTHESIS AT CITY OF HOPE FOR GENENTECH

Interviews Conducted by
Sally Hughes
in 2005

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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Dr. Keiichi Itakura, May 2006

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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 prweserving 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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November 2005

ORAL HISTORIES ON BIOTECHNOLOGY

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

Paul Berg, Ph.D., *A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry*, 2000

Mary Betlach, Ph.D., *Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory*, 2002

Herbert W. Boyer, Ph.D., *Recombinant DNA Science at UCSF and Its Commercialization at Genentech*, 2001

Roberto Crea, Ph.D., *DNA Chemistry at the Dawn of Commercial Biotechnology*, 2004

Donald A. Glaser, Ph. D., *The Bubble Chamber, Bioengineering, Business Consulting, and Neurobiology,* 2006

David V. Goeddel, Ph.D., *Scientist at Genentech*, CEO at Tularik, 2003

Herbert L. Heyneker, Ph.D., *Molecular Geneticist at UCSF and Genentech, Entrepreneur in Biotechnology*, 2004

Keiichi Itakura, *DNA Synthesis at City of Hope for Genentech*, 2006

Irving S. Johnson, Ph.D., *Eli Lilly & the Rise of Biotechnology*, 2006

Thomas J. Kiley, *Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur*, 2002

Dennis G. Kleid, Ph.D., *Scientist and Patent Agent at Genentech*, 2002

Arthur Kornberg, M.D., *Biochemistry at Stanford, Biotechnology at DNAX*, 1998

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George B. Rathmann, Ph.D., *Chairman, CEO, and President of Amgen, 1980–1988*, 2004

Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders (Hugh D'Andrade, David Holveck, and Edward Penhoet), 2001

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William J. Rutter, Ph.D., *The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco, volume I*, 1998

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

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William Young, *Director of Manufacturing at Genentech*, 2006

Oral histories in process:

Brook Byers
Ronald Cape
Stanley N. Cohen
James Gower
William Green
Daniel E. Koshland, Jr.
Arthur Levinson
Arthur Riggs
William J. Rutter, volume II
Mickey Urdea
Pablo Valenzuela
Keith R. Yamamoto

Interview History—Keiichi Itakura

These interviews with Keiichi Itakura, a professor in the Division of Molecular Biology at the Beckman Research Institute of the City of Hope Medical Center in southern California, are included in the oral history series on Genentech because of his seminal contributions to Genentech's three earliest research projects. At a time in the 1970s when scientists with the capacity to synthesize DNA by entirely chemical means were few and far between, Itakura and Arthur Riggs, his colleague at City of Hope, conceived of combining DNA synthesis and recombinant DNA with the aim of constructing and reproducing genes that would code for useful proteins.

The interviews describe Itakura's education in Tokyo in pharmaceutical science, his postdoctoral work in Saran Narang's DNA chemistry laboratory in Canada, and his subsequent employment at Caltech and City of Hope. It was in Narang's lab that he developed an improved method for synthesizing DNA and laboriously constructed a genetic regulatory element, the lac operator. It was research with Herbert Boyer's group at UCSF, implementing Riggs' idea of using the then-novel technique of recombinant DNA to replicate Itakura's chemically constructed DNA fragments, that showed for the first time that synthetic DNA was biologically functional. The success led to a second collaboration, in 1976, this time on the hormone somatostatin, a project financed by Genentech, a company founded that year by Boyer and the venture capitalist Robert Swanson. The successful construction, cloning, and expression of the somatostatin gene in 1977 led immediately to research on human insulin and then on human growth hormone. By 1979, Genentech could claim success in constructing, cloning, and expressing all three genes. The work not only proved the utility of the combined technologies but was critical to Genentech's survival as an entrepreneurial startup and a forerunner of the biotechnology industry. In addition, a series of exceedingly broad and valuable patents on the methodology eventually issued.

But not everything was smooth sailing. Itakura tells of a political disagreement with a senior professor in Tokyo that led to his departure for Canada, where again tension arose with a superior. Predictably, the research for Genentech did not always proceed seamlessly, requiring revisions, some of which Itakura outlines in this oral history.

Two interview were recorded in Itakura's office in the City of Hope's Molecular Genetics Laboratory, which he heads. Prompted by ongoing litigation with Genentech, City of Hope required that Gordon Goldsmith, the institute's legal counsel, attend each interview with Itakura (and also with Riggs). Goldsmith was a largely silent observer at all five sessions, in only a very few instances halting discussion, mainly regarding the disputed contract between City of Hope and Genentech. Itakura's Japanese roots are apparent in his idiosyncratic but expressive English, which was slightly edited to clarify his meaning. Itakura reviewed the interview transcripts, making very minor changes. The transcripts

with his corrections and additions were then sent to Goldsmith and Gregory Schetina, chief deputy general counsel for the institute. Neither attorney requested changes. By agreement with Genentech regarding the oral histories it supports, its legal department received transcripts of these interviews and all interviews in this series to review solely for current legal issues. As in all instances to date, no changes were requested. Itakura remains an active scientist, content that City of Hope leaves him free to pursue basic research, currently on the relationship between cancer and obesity. This oral history of a pioneer of DNA synthesis complements a number of oral histories in this series, particularly that of his collaborator Arthur Riggs, and adds significant participant information on the three earliest research projects at Genentech.

The Regional Oral History office, a division of the Bancroft Library, was established in 1954 to record the lives of individuals who have contributed significantly to the history of California and the West.

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April 2006

Note: Gordon Goldsmith, counsel for the Beckman Research Institute, was present at the interviews and occasionally commented.

Interview #1: January 12, 2005

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

Hughes: Please tell me your family background, starting with your grandparents.

Itakura: They said a couple generation before they are the samurai.

Hughes: Really?

Itakura: Yes, and they made mistakes, and they are fired, and they became farmers. That's my father's side. I never met them, on my father's side. Then mother's side, I remember grandmother, but I never met grandfather; he died very young. They are somehow rich people, but lost the money for gambling. Grandfather likes drinks a lot and gambles a lot, so there goes the money.

Hughes: Does that mean that your grandmother was poor?

Itakura: Not necessarily poor, but she raised four girls, including my mother. She seemed to work hard, so maybe not poor but not rich.

Hughes: What did she do?

Itakura: I don't know. But at the time I remember her, the old [adult] four girls working already, so I don't know exactly what she did.

Hughes: Was it unusual in that era to have all four daughters working?

Itakura: Yes, is very unusual. Usually girls did not work, just to stay home, only supporting husband or whatever, and then raising the kids.

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

Hughes: What did your mother do?

Itakura: Pharmacist.

Hughes: Did that require a degree?

Itakura: Yes. You have to go to school four years to get the license for the pharmacist. She's almost ninety years old [now]. [Only] a very unusual girl went to the pharmaceutical school. Many girls, as I said, stay home and raise the kids, supporting husband, and she went to pharmaceutical school.

Hughes: Do you know what her motivation was?

Itakura: [pause] I don't know; I have no idea.

Hughes: Does she have a scientific bent?

Itakura: No, I don't think so. Maybe used to have one—

Hughes: Not anymore?

Itakura: Not anymore. [laughs]

Hughes: And then what about your father?

Itakura: Father is the last son of the farmer, and he only graduated middle school.

Hughes: Which is like our high school?

Itakura: I guess. Maybe the middle school is between elementary school and high school.

Hughes: So he had not much education?

Itakura: Not so much education. They are much poor because are farmer, and many brothers and sister, maybe six brothers and sisters, and then he had to leave the farm and then go somewhere and work.

Hughes: What work did he do?

Itakura: I think, he came to Tokyo and worked for the pharmacy.

Hughes: Is that where your parents met?

Itakura: Yes, somebody arranged for them to meet. As far as I know, first time they met and she said no, and then a second time they met and then a yes. So that's life. [laughter]

Hughes: Did the difference in family status make a difference? She came from what used to be a well-to-do family and he was a farmer.

Itakura: Yes, that used to be a big trouble, and still they have a problem in Japan but somehow overcome.

Hughes: Did they both continue to work when they began to have children?

Itakura: Yes. Somehow they saved money, and they started the one small pharmacy and—

Hughes: This was in Tokyo?

Itakura: Yes, in Tokyo. And then we have five brothers and sisters, before the Second World War, so government promote to have many, many babies and have kids.

Hughes: You got a financial incentive?

Itakura: I don't know—I was a kid; I don't remember! [laughter] But they were very successful running pharmacy, so I think they had enough money, even with five kids.

Hughes: And where are you in birth order?

Itakura: Second.

Hughes: And are you the oldest boy?

Itakura: Pardon me?

Hughes: Are you the oldest boy?

Itakura: Yes, the first son, and supposedly I'm the most needed kid of the five kids.

Hughes: So they put their resources into you?

Itakura: Yes—well, also I'm very much interested in the science, that's why.

Hughes: That became obvious very early, yes? What was it like living in the family? Were you a close family? Did you do a lot of things together?

Itakura: Yes, we used to be when we were small kids, maybe up to ten, fifteen years old. Big family, and always we were fighting for eating and fighting for something. But also my mother has three sisters, and one sister adopted my younger sister.

Hughes: Why was that?

Itakura: I don't know exactly.

Hughes: She didn't have children of her own?

Itakura: No, she don't marry.

Hughes: And she wanted a child.

Itakura: Most likely, but I have no idea.

Hughes: Was that upsetting to you, to lose a sister in a way?

Itakura: No, because sister lives very nearby, just five or six miles away, in walking distance. So not necessarily [upsetting].

Hughes: Where did you go to school?

Itakura: The elementary school, you mean?

Hughes: Yes.

Itakura: Just the elementary school nearby.

Hughes: A public school?

Itakura: Yes, public school. Then the middle school and high school I went to a private school. At that time, [it was in] the top ten private schools. Actually, that's more than fifty years ago. But now [it's] the best private school in Tokyo.

Hughes: Was it competitive to get into in your day?

Itakura: Yes, very, very competitive. You have to study five, six hours every day, but I hate the studying.

Hughes: You were sent there by your parents because it was obvious that you were very bright?

Itakura: I guess so, but as I said, I don't like to go to that kind of private school.

Hughes: You were happier at the public school?

Itakura: Yes, public school is probably much better for me, because the friends are always nearby. If you go to private school, many people come from many places. So once you get home, nothing to do, just to study. At that time, middle school and high school, I don't like to study. Every teacher ask, "Memorize this, memorize this." My memory's good, but I don't like to just memorize. And only I studied science.

Hughes: You mean, you worked in science because you liked it?

Itakura: Yes, I like science, but I can't do only science; [I have to] study the language and the social [studies] and the so on so forth—with a really bad grade.

Hughes: Because you didn't work.

Itakura: Right. I was borderline.

Hughes: But science you did very well?

Itakura: Yes, science I tried to get always A grade.

Hughes: What branch of science did you become interested in?

Itakura: [In Japan] they teach almost everything [in high school]: chemistry, physics, biology. Here you take only chemistry, maybe sometimes biology, in the high school; you don't need to take all of them.

Hughes: Is that still true, that Japanese high school students have to take all the sciences?

Itakura: That is now changing, so depends on university you are interested in. In high school, you can select. Maybe you can take only chemistry or maybe you can take only physics.

Hughes: What was most interesting to you?

Itakura: Chemistry. Particularly the experimental part of chemistry, mixing A and B and then color change or something like that.

Hughes: So inorganic chemistry?

Itakura: Not necessarily, just generally speaking chemistry.

Hughes: You liked working with your hands?

Itakura: Used to be. [laughs] Not any more for me.

Hughes: You were interested in the laboratory part of science, rather than the conceptual side of science.

Itakura: Not necessarily. Actually, I like both. Just mixing A and B and C is probably already known. You have to find out something new always. In other words, I don't want to be a technician. You have to think about what is important; why we carry out the experiment. So I like the thinking.

Hughes: Were you thinking that way, even as a student?

Itakura: You mean a high school student?

Hughes: Yes, that you didn't want to just do routine science; you wanted to have a creative part in it?

Itakura: No, at that time probably I was asking why, why, why?—that's all. Learning is more important at that time, and they emphasize memorization.

Hughes: I notice your degrees are in pharmaceutical science.

Itakura: Yes, that's correct.

Hughes: Why not chemistry?

Itakura: Well, as I said, I don't study in high school, so the going to [a good] school, particularly for the engineering school or science school, is very difficult to go into because the testing included not only science, but language—English, and so on. So you have to take many, many items, and I can do only science, so probably cannot pass the test that's very difficult.

Hughes: Did you try?

Itakura: Yes, I tried, and I failed, obviously. [laughs]

Hughes: In pharmaceutical science you could take the entrance exam just in the sciences?

Itakura: Yes. I remember that's only English and chemistry and mathematics. So that's not so bad.

Hughes: Your English was all right?

Itakura: I can read, at that time I could read it, so that's no problem.

Hughes: Yes, yes, all right.

Itakura: Also the other reason might be—might be, I'm not sure. At that time my parents ran four pharmacies, so maybe I can—

Hughes: Help out?

Itakura: Help out, that's a possibility, but I was not sure that was true or not.

Hughes: Were you interested in pharmacy, when you got into school?

Itakura: No. [laughs] At that time, maybe thirty, forty years ago, they emphasized chemistry. That was not so bad. Actually, I can learn more chemistry, in particular. Organic chemistry was the strongest field of the pharmaceutical school at that time.

Hughes: So that was good for you?

Itakura: Yes, it was.

Hughes: Had you considered going anywhere else other than the Tokyo College of Pharmacy? Was that the only place where you applied?

Itakura: Only one place they take [me].

Hughes: [laughter] It was a simple decision.

Itakura: That's right, very simple.

Hughes: Were there any teachers that you particularly had a relationship with?

Itakura: Pharmaceutical school?

Hughes: Yes, anybody that was influential?

Itakura: Yes, the fourth year we usually go to the lab work, maybe only three, six months. One professor he was very influential. He is a very old organic chemist, and he's not necessarily nice guy. [laughs] He taught me organic chemistry.

Hughes: In class, or did you have some outside instruction?

Itakura: In class was quite boring; he's just reading the textbook.

Hughes: But was he in the laboratory?

Itakura: In laboratory, yes.

Hughes: And so you made sure that you had time with him?

Itakura: That's what I did. After the graduation [1965] I went to his—what do you call this; there is no English correspondent. I went to his lab for graduate study, and there I learned more organic chemistry.

Hughes: How much freedom did you have in his lab to do what you wanted to do?

Itakura: I had lots of freedom, and I can do whatever I want, and all the experiments were my own idea. Of course from time to time I discuss with my professor. But always he said, "Okay, go ahead."

Hughes: Was he like that with everybody, or did he think you were special?

Itakura: They started [the] graduate school one year before I started, and he doesn't have any graduate students, so I'm the first graduate student. I'm not sure if that's special or not. But I was very lucky because he gave me lots of freedom, yes.

Hughes: What did you work on?

Itakura: The chemical synthesis of the alkaloids.

Hughes: Why did you choose that field?

Itakura: Because my professor was very familiar with that kind of work, and he got the Ph.D. in the same area. So I thought that probably I [would have] the best education and training in the same area.

Hughes: Anything more to say about education?

Itakura: University?

Hughes: Anything that might have given you direction in what was going to come later in life.

Itakura: In the college, probably, I usually don't attend the classes.

Hughes: This is a pattern. A pattern of negligence! [laughter]

Itakura: Because the classes very boring. For example, the teacher in biochemistry, he faced the blackboard just writing the formulas—write and write and write, never facing the students. So I don't listen; I skip.

Hughes: Was this typical of Japanese higher education at that period?

Itakura: Not necessarily, some classes quite bad, some classes very good. Even if I don't attend [classes], I can graduate—just pass the test. So I have lots of time to do something else. [laughs]

Hughes: And what did you do?

Itakura: I like sports, so I play lots of the sports.

Hughes: Such as?

Itakura: Running, and also—it's not popular in the U.S.—I play rugby.

Hughes: Rugby was popular in Japan?

Itakura: Yes, very popular in Japan.

Hughes: More than soccer?

Itakura: Used to be more than soccer, but now soccer is more popular. What else I did in the college?

Hughes: Were you living with your family?

Itakura: Yes, because that's only three, four miles from college.

Hughes: I see.

Itakura: That's typical, actually. If you live in Tokyo and then went to university or college in Tokyo, usually you live with your parents; doesn't cost anything.

Hughes: Well, you graduated in 1970 with a Ph.D. in pharmaceuticals science, and then in 1971, all of a sudden you're in Canada?

Itakura: Yes.

Hughes: Tell me how that happened.

Itakura: It was another problem. [laughs] [pause] How to explain? In the Japanese system, the head [of each lab] is a professor, and the next one is associate professor, and sometimes assistant professor, and lecturers. So four/five [senior] people in one lab, and that's [the] order, and then you have to step by step go up to become professor. At that time [the professor] almost retire, so the one position was open, but the associate professor, I have a problem with him, not only [over] science, but I have a conflict with his politics.

Hughes: What kind of politics?

Itakura: At that time, many people thinking anti-establishment. But I'm not so anti-establishment, but very sympathetic to the anti-establishment. Associate professor, he doesn't like the anti-establishment politics. Was all very similar to

the U.S. situation, that anti-war movement against the Vietnam War. I am against the Vietnam War, too. So those the kinds of politics, and he doesn't like me to stay in the same lab. So I have no choice [but] to pick somewhere to go and then find out to what place.

Hughes: How did he know about your politics? Were you were in protests?

Itakura: Not necessarily protests but some kind of meeting. Then [I] express my opinion, and it was always trouble with him.

Hughes: Did that surprise you, that he would ask you to leave?

Itakura: No, not necessarily, because if I stay with him then always we have to fight.

Hughes: But if your science was good then that could have been enough. It was a scientific laboratory after all, not a political department.

Itakura: Yes, that's what my professor told me, that I should stay because the science is okay; science is good enough. But associate professor doesn't think so. So big conflict.

Hughes: So then you were forced to go—

Itakura: Not necessarily forced to go. I more interested in going because the system in Japan at that time is very bad.

Hughes: Very hierarchical?

Itakura: Yes, and if you work on something important, establish something, or find something new, you have to publish the paper with that guy, associate professor, and so I don't like to do that. Also probably less freedom than I expected, written or thinking, and I'm very much interested in going out and seeing how much I can do or what I can do. Then I applied to a couple of places, one in the Switzerland, one in the Canada.

Hughes: Why those two places?

Itakura: The [one in] Canada is the National Research Council of Canada, and in Switzerland is one of the best technical schools, just like Caltech. Then I got offer from Canada. So very simple, just one choice.

Hughes: Did you actually apply to the Swiss institution?

Itakura: Yes, I apply, and then they don't have enough money, only fifty percent, the professor said they could provide.

Hughes: What was the institution? You can say it in German.

Itakura: Hochschule. I don't even remember.

Hughes: Hochschule literally translates to high school, though it was probably not a high school in the American meaning.

Itakura: That's right..

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

Itakura: [The head of the lab,] his name is Dr. [Sarang] Narang, and [I went] because I wanted to learn how to chemically synthesize DNA. The other one in Switzerland is not DNA—they synthesized peptides. So there is an automatic choice which one is more important, peptide or DNA, and I pick DNA.

Hughes: Why and when did you become interested in DNA?

Itakura: Maybe when I was in graduate school, 1968,'67, Dr. [Gobind] Khorana publish—I think not publish—according to newspaper, the title is, "Dr. Khorana Synthesizes Life." That means probably DNA, and [he] actually synthesized gene for tRNA [transfer RNA], so maybe he synthesized a part of life. That then probably make me start being interested in synthesizing DNA. That's probably one reason. At that time I'm not so much familiar with the biology, even though I start learning the molecular biology with a couple of people from the school.

Hughes: In Canada?

Itakura: No, in Japan, when I was a graduate student. A couple of friends in graduate school, they are studying biology, and once a week we get together and learn molecular biology. At that time in Japan there is no class they teach in the molecular biology, so we buy the book and then study.

Hughes: As soon as the double helix structure was worked out, scientists in many parts of the world became focused on DNA. What was happening in Japan?

Itakura: They have a very small group that study the molecular biology, and one of the persons is Dr. Susumu Ohno here. Actually, he died about three or four years ago. He's one of the pioneers in Japan to study molecular biology. So only very, very few people did research on molecular biology. I think almost all research was done in United States.

Hughes: Did you think of yourself as a molecular biologist at that point?

Itakura: No, I am a chemist.

Hughes: So you were a chemist working with DNA?

Itakura: Oh, no. In Japan, I was not a chemist on DNA, I was working on alkaloid. Then I switched the field in Canada to DNA.

Hughes: Oh I thought you said that while you were still in Japan you and your friends—

Itakura: [James D.] Watson publish the book, first edition—I don't even know the name.

Hughes: *Molecular Biology of the Gene*.

Itakura: *Molecular Biology of the Gene,* yes. And we are very much interested in molecular biology, what is the molecular biology, but we have no knowledge. Three graduate students got together without any teacher because the teachers—I mean the professors—they don't know anything about molecular biology. So we got together and studied the book.

Hughes: There was nobody on the faculty interested in DNA?

Itakura: No, not at that time.

Hughes: You knew about Narang from reading some of his papers?

Itakura: When I applied to the National Research Council of Canada for the postdoc fellow position, they listed the names of the labs and what they are doing. So that's why I knew that Dr. Narang, in the list of the lab chief, lab head, was working on the DNA chemistry.

Hughes: So your off-hours interest in DNA in Tokyo then became something that you could actually work in and do in Canada. You had made the decision that DNA was where you wanted to apply your chemistry?

Itakura: Yes, that's why I went to Canada.

Hughes: Tell me what you found when you went there?

Itakura: It's cold. [laughter] It's located in Ottawa, that's the second coldest capital city in the world. Actually, National Research Council is a very small research institute, I don't know how many groups, maybe twenty groups in the biology [division], and one group has maybe one, sometimes two, sometimes three people, maximum five people working with lab head. A kind of family-type formalization—strange expression. When I started, Dr. Narang has only one postdoc fellow, that's me and technician, so that's the beginning. He actually learned DNA synthesis from Dr. Khorana. The method he was using is very, very—what they call, classic?—very slow.

Hughes: This is the diester method?

Itakura: Yes, diester method.

Hughes: Which is Khorana's method?

Itakura: That's right, yes.

Hughes: And Narang had been a student of Khorana?

Itakura: Yes. He was a postdoc fellow with Dr. Khorana.

Hughes: Where was Khorana?

Itakura: First he was in Vancouver, the University of British Columbia, and then moved to Wisconsin. When Narang is in Khorana's lab, that is in, I think, Wisconsin. Then he found a job in Canada, National Research Council.

Hughes: So Narang and Khorana were in different places by the time you arrived in Canada.

Itakura: Yes. But they don't like each other. [laughs] Actually, Narang, he doesn't like Khorana.

Hughes: Why?

Itakura: He's always complaining about Khorana, particularly Khorana pushing to work twenty-four hours a day, even the weekend.

Hughes: It took something like forty man-years to build the first synthetic gene?

Itakura: Yes, he spent four or five years, with about ten postdoc fellows, according to Narang. They work twenty-four hours a day, seven days a week.

Hughes: Narang one of his prize students?

Itakura: Yes. I think he was involved in making the gene for tRNA.

Hughes: When you got to Narang's lab, what was he doing?

Itakura: It was not so clear, actually. He tried to improve a DNA method, a method. He tried to improve the chemistry of the DNA synthesis because he doesn't have enough manpower, enough money, because NRC does not provide lots of funds. So he just hired one technician and one postdoc fellow. So he just tries to carry out the improvement of DNA synthesis, essentially chemistry.

Hughes: Khorana didn't have that impetus because he had plenty of people. But still, presumably he would have liked to have done it more efficiently. Was Khorana trying to improve his method as well?

Itakura: Yes, probably 1960, at that time he is, but not so significantly. After synthesize gene for tRNA, he switched the field. I think he switched to the neurosciences. So he stopped making DNA around 1970, end of 1970 I believe, and then switched the field

Hughes: So who besides Narang in the early seventies had DNA synthetic capability?

Itakura: In U.S.—1970, hmm. Actually not so many, maybe [Robert L.] Letsinger, at Northwestern University.

Hughes: Yes, I've heard that name. Is he a chemist?

Itakura: Yes, he's a chemist. And in Europe, maybe a couple groups.

Hughes: Herb Heyneker mentioned [Hubert] Köster—

Itakura: Yes, Köster. But maybe he's not already 1970; probably he start working on DNA synthesis late 1970, I believe.

Hughes: Herb Boyer knew somebody in Germany before he knew you.

Itakura: He was in, I believe, in the U.S. Yes, I think—

Hughes: Originally, the idea was that Peter Seeburg would come to Boyer's lab to synthesize DNA, not to [John] Baxter's lab, where he ended up. Where did Seeburg come from?

Itakura: Köster.

Hughes: What laboratory was Seeburg in?

Itakura: I don't remember, but the possibility is only one—Köster.

Hughes: Anyway, there weren't very many people doing DNA synthesis.

Itakura: That's right.

Hughes: Okay, so then you came to Narang's lab, and what did you do?

Itakura: First maybe six months, I learned the method he was using that's called diester approach. I found out that it is tedious, time consuming, and very bad chemistry. I'm a chemist, so immediately I can tell you that was a very bad chemistry. After

the reaction, you got many, many side reactions—even the yield is less than fifty percent, sometimes ten percent. So spending lots of time on the purification of the product to go to next step. So I tried to improve the chemical DNA synthesis. I read lots of journals, books, and then try a couple methods. One is triester method; the other one is called phosphite approach, which was not working. And then phosphotriester method works very well.

Hughes: Was that an existing method?

Itakura: Yes. The phosphotriester is kind of existing, just one, only one, paper? Maybe two, a couple of papers only published.

Hughes: And working with DNA?

Itakura: Yes.

Hughes: Who had done that earlier work?

Itakura: Dr. [Colin B.] Reese, in England.

Hughes: To you as a chemist, would it be obvious if you found problems with the diester method that you would be interested in the triester?

Itakura: Yes, because the organic chemists usually don't like the products soluble in the water.

Hughes: Why?

Itakura: Well, the very simple answer is we are not familiar with the working, the biology, in the water. Almost everything soluble in the water, so almost every reaction is carried out in water. But organic chemists usually using organic solvent, like benzene, chloroform, which [does] not mix with water. And [for] the purification method, we are always using organic solvents instead of water. And the technique at that time, the purification using water, is very tedious, time consuming. But if we use organic solvent, the purification is much faster, and you can purify huge amounts compared to purification using the water.

Hughes: So that makes sense: DNA is a biological substance. Presumably somewhere down the line, you would be using this technique in biological matrix, biological substrate. Did it worry you that you were now using a method that wasn't water-based?

Itakura: Yes. For example, some kind of the functional group, particularly in case of DNA the connection between the two units of the base is a phosphate, which cause the DNA [to be] soluble in water. So we protect that phosphate, and that becomes soluble in organic solvent. At the end, we can remove those protecting

group or masking group, then it becomes soluble in the water. So that's not necessarily specific technique; that's already developed in many, many organic synthesis, like peptide synthesis. So that's not a problem.

Hughes: How long where you there?

Itakura: Three, three and a half [years].

Hughes: So '73 to '74, because in '74 you went to Caltech. How did Narang feel about your improvement?

Itakura: He was very excited about our result, because we can make DNA very quickly, maybe five to ten times faster, so he was very happy. Now one more thing is very important: we also develop not only method but the chemicals to the connecting or coupling of two units of DNA. Also we develop [the method] in a very efficient way, and then we have less side reactions, so more efficiently we can connecting the DNA unit.

Hughes: And you did that?

Itakura: Myself, and also my coworker. At that time we publish more paper, so Narang has more money and hired one more person.

Hughes: What nationality is Narang?

Itakura: Originally, India, and then I think Canada.

Hughes: Did you get along well with him?

Itakura: Well, not big problems. I just don't worry about the politics, just the science. His wife was—I don't like her [laughs]. For example, she [mixed] the public and personal. We working only science, not only from the personal problems. One summertime, they were making a swimming pool, and they ask us to help. [laughs]

Hughes: You were supposed to go out and do hard labor?

Itakura: Also, everyday, five o'clock, she call Narang. It's amazing.

Hughes: And you went?

Itakura: No. [laughs]

Hughes: You put your foot down.

Itakura: That's right.

Hughes: Oh dear. There was some work that seems to be very important for what came next. That is, working with Narang, you synthesized the lac operator. Is that right?

Itakura: Yes.

Hughes: Well, tell me about that work and how it might relate to what comes next.

Itakura: At the end of the second year of postdoc fellow[ship], and according to NRC, I can stay only two years, and postdoc fellow terminates usually at the end of two years. So I try to find a job, and I send about ten letters to mainly the U.S. universities—Stanford, and Berkeley, City of Hope, and many other places. Then I send a letter to Dr. Ohno, and then Dr. Ohno pass the letter to Dr. [Arthur] Riggs. Dr. Riggs at that time was working on lac operator, so he was very much interested in getting large amounts of lac operator, because he was working with Dr. [Richard] Dickerson at the Caltech. He was very much interested in crystallizing the complex, lac operator and lac repressor.

Hughes: But you hadn't been working on the lac operator in Narang's lab?

Itakura: That's correct.

Hughes: The triester method was the main thing that you did with Narang?

Itakura: Yes. Then I start communications with City of Hope. And then I got an interview at the City of Hope and also the Caltech because of Dr. Dickerson. Then at that time when we came to City of Hope, Dr. [Rachmiel] Levine is medical director. And I remember the meeting. He is very much interested in making the gene for insulin, because he is an expert of the diabetes, and he discovered insulin receptor for the first time in the world.

Hughes: When would this be?

Itakura: '74.

Hughes: Yes, because in '74, you become a senior chemist at Caltech.

Itakura: [counts]. Yes, okay. Sometime in '74 I got the job. I believe the salary come from the Caltech. First I got the job offer from Caltech, because the City of Hope did not have any facility for chemistry. So I was supposed to go to Caltech, but I was waiting for a visa to work in the U.S. So I spend waiting, maybe seven months, six months.

Hughes: You had to stay in Canada?

Itakura: Yes, I had to stay in Canada because I have to get the visa. That's why even after two years I stay in the Canada.

Hughes: And you continued to work in Narang's lab?

Itakura: Yes, but—

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

Itakura: I finally got visa May '75, and then I moved to California. So probably seven months, eight months, after I got the offer from Caltech. Even after I got the offer and I got the salary from Caltech, I stay in Narang's lab in Canada and making the lac operon. And I came to the California with lac operon.

Hughes: Was that a labor of love? Was it very tedious to make the operon?

Itakura: Well, yes and no.

Hughes: How big is it?

Itakura: It's a 21 base-long DNA. And I did everything by myself, so in a sense that's tedious.

Hughes: So no lab assistants?

Itakura: Right. Nothing, and just doing everything by myself. And then supposedly I make the milligram amount, but I make very small amount only. So we decided to clone it in the bacteria, and then show it biologically functions. And then we start collaboration with [Herbert W.] Boyer, UC San Francisco.

Hughes: Well, stop for a minute; let's pick up some things here. When did you have the meeting with Dr. Levine?

Itakura: When I visit in 1974. I think '74, the springtime?

Hughes: It would have been your first visit to the United States, wouldn't it?

Itakura: That's right, yes. At the same time, I visited to Dickerson. So I think '74, springtime, yes I believe.

Hughes: So that is as far as you know the first time that somebody mentions synthesizing human insulin?

Itakura: As far as I remember, yes, this is the first time to discuss with somebody to make it.

Hughes: You hadn't thought about this kind of thing yet?

Itakura: Yes, because that was my dream making a gene, so maybe insulin gene, or whatever gene. I'm not sure—

Hughes: Had you thought of insulin?

Itakura: I think yes, making gene for insulin—

Hughes: Before you talked to Dr. Levine?

Itakura: Yes, I think so, because what kind of gene you want to make? I didn't write anything—the note, or anything. But I was thinking making gene, and maybe insulin; that's probably quite obvious.

Hughes: Well, not necessarily, because look at what Khorana had done—he'd synthesized a transfer RNA, not practical.

Itakura: Yes, that's not practical.

Hughes: When was the idea of being able to synthesize DNA connected to the idea of practicality: we can not only do this wonderful thing, but we can make it useful?

Itakura: Khorana was working on the codon. Essentially, he got the Nobel Prize for the genetic code, and then he pretty much was interested in tRNA, because that carry the anti-codon. So his background is the basic science, but my background is more pharmacy. Not only biologically but medically important things is always my interest. But not exactly insulin, I'm not sure. But one of them is probably insulin.

Hughes: So at the meeting which Dr. Levine attended when he said "insulin," that made a lot of sense to you?

Itakura: Yes. He was asking, how long would it take to synthesize a gene?

Hughes: That was maybe not a big gene, but it was bigger than anybody had ever synthesized, right?

Itakura: That's correct, right.

Hughes: Did that worry you?

Itakura: No, the A-chain is twenty amino acid, the B-chain is thirty amino acid, so probably about 150 bases.

Hughes: You would synthesize the chains as two separate elements?

Itakura: Well, actually at that time I didn't think about it that way, A-chain, B-chain, C-chain, but about 150 to 100 base long.

Hughes: Did you even know about an A- and B-chain?

Itakura: Well, of course, what is insulin? [laughter]

Hughes: You came to Caltech first, right? Dr. Riggs told me this morning that your appointment was actually to be at City of Hope, but City of Hope did not have lab space for you yet, so they paid for you to be at Caltech.

Itakura: Okay, maybe I have some confusion, because Caltech pays some part of my salary and at that time maybe City of Hope also pay my salary; I don't know exactly.

Hughes: Well, it sounds as though Caltech paid for your work in Narang's lab, right?

Itakura: Yes.

Hughes: But you think maybe once you came to California that both institutions paid your way?

Itakura: I'm not sure that's the transition. Only I remember is I'm first paid by Caltech and then City of Hope. I don't know exactly when they change.

Hughes: Tell me what you found at Caltech. You were in Dickerson's lab, or you had your own separate lab?

Itakura: No, Dickerson's lab.

Hughes: And so you had to set up the apparatus for DNA synthesis, right?

Itakura: That's correct, yes.

Hughes: Was that easy enough to do?

Itakura: Yes, that's not so difficult and very efficient, and much quicker than NRC [National Research Council]. NRC is the government, so kind of slow. For example, technician usually work nine to five and then go home. But Caltech, even sometime technicians stay very long time, and also the Caltech graduate student work very hard. They usually come nine o'clock, ten o'clock, and then six o'clock go home, and after eating, come back and work until midnight. So that's very exciting place, and lots of seminars, and interaction between the groups is very active, so I think very nice place to work.

Hughes: And you took advantage of all this interaction?

Itakura: Actually, I didn't start any collaboration at that time. Yes, many visitors come, so yes, I think I did [have interactions]. I think very nice experience working at the Caltech, yes.

Hughes: Now Dickerson was an x-ray crystallographer, so presumably he didn't have too much direct input with what you were doing. You were the DNA synthesis person in a lab that was an x-ray crystallography lab. Were you pretty much working on your own?

Itakura: Yes.

Hughes: Was that all right?

Itakura: Yes, that's okay, that's no problem. Actually, I enjoyed the freedom in Dickerson's lab, and he was not going to tell me what to do, and that's very good. But in Canada, because Narang is a DNA chemist, so always we have a meeting and what to do. But we usually don't listen to him [laughs], and I do it my own way.

Hughes: So it was nothing new really to go to Dickerson's lab—you were used to working on your own.

Itakura: That's right.

Hughes: How does Richard Scheller come into the picture?

Itakura: He's a young, very enthusiastic graduate student and very smart guy, and working very hard, yes. He's one of my best friends, is still, and yes, he influenced me a lot, and also I influenced him.

Hughes: How did he influence you?

Itakura: The way to thinking about science. The graduate student in Japan, they usually do whatever professor says, and many, almost all, graduate student do not have their own project or Ph.D. thesis. But Richard Scheller, one of my friends, he decides what he wants to do. He will not so much be related to the Dickerson's project, because he is obviously not x-ray crystallographer; he's was not interested. So given he is not x-ray crystallographer, he came to Dickerson as a graduate student, and he was more interested in the biology. And also, he would like to use DNA chemistry, the oligonucelotide synthesis for the biological problems. And we published one paper using oligonucleotides for biological research.

Hughes: Is that the linkers paper?

Itakura: Yes, the *Science* paper.

Hughes: Do you remember the year?

Itakura: [flips through papers] '77.[2]

Hughes: I talked to Scheller, very soon after he became vice president of research at Genentech. Was it before you came that Scheller was involved in synthesizing part of the somatostatin gene?

Itakura: No. After I moved to City of Hope we started the somatostatin project.

Hughes: He told me that whatever he was synthesizing didn't work out.

Itakura: Yes, okay, that's one problem—he has no background of chemistry. So when I work together with him [on] DNA synthesis, going through step by step, and then each time you have to check the step, so I know exactly what he is doing. But when I left [Caltech] and come to City of Hope, and he was on his own, he has a very difficult time making DNA.

Hughes: Why were you relying on him? City of Hope now had you, the master of DNA synthesis.

Itakura: That's [because] he wants to be involved in somatostatin gene synthesis. He was very ambitious. He wants to make DNA; he wants to express [somatostatin] in the bacteria, and so on. So he's a very enthusiastic scientist. I like him that way. [laughs]

Hughes: But when it didn't work out, he then dropped out of the somatostatin project, did he not?

Itakura: That's correct, yes.

Hughes: Yes, that's the end of it. But that also explains why there's a contract with Caltech. Genentech had a contract with Caltech because of Richard Scheller, not because of you.

Itakura: That's correct.

Hughes: By the time the somatostatin project starts, you're back here.

Itakura: Yes. That's also his different style [from the Japanese]. Even though he is in the x-ray crystallography lab, he would like to work on DNA synthesis, synthesize somatostatin. In Japan that's impossible.

Hughes: Yes, and I think I know which system you like better.

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2. See Itakura's curriculum vitae in the appendix.

Itakura: [laughs] Of course.

Hughes: Would you have liked to have stayed at Caltech? [tape interruption] You said it was a very stimulating place.

Itakura: No, because I'm more interested in working on the gene synthesis for something medically important. At that time we discuss all the ways to express in the bacteria and see what happened. So that project I'm more interested in.

Hughes: Could we go back to the lac operator work for a minute? When you synthesized the lac operator in Narang's lab, did you prove that it was functional?

Itakura: No. I just synthesized.

Hughes: You proved the lac operator was functional with the Boyer group?

Itakura: Yes. We collaborate with Boyer's group, in particular [Herbert L.] Heyneker. Heyneker was working on it day and night.

Hughes: He was pretty fanatic, wasn't he?

Itakura: Yes, at that time.

Hughes: Was the UCSF group pretty much working in their lab and you were down here, or was there a lot of movement?

Itakura: In the case of lac, no, not so much movement. They cloned at UC San Francisco, and then they express over there, and then they got the so-called blue colony, and then they just call [us at City of Hope]. So almost no interaction at that time.

Hughes: Why is Narang on that paper?

Itakura: Ah, because I was in Canada when we start the synthesis. Actually, I finish the synthesis of lac operon in Canada in Narang's lab. So that's why.

Hughes: So you were using that material?

Itakura: And also we discuss the project.

Hughes: What about the Caltech people? Dickerson, and who else is on there?

Itakura: [John] Rosenberg?

Hughes: When was that paper published?

Itakura: '76. [long pause, paper shuffling] Yes, Rosenberg.

Hughes: Why is he an author?

Itakura: Actually he was involved in the x-ray crystallography study of lac operon and repressor.

Hughes: So that information was used in this work?

Itakura: [laughs] I don't know. No, not necessarily. But he is a major force for the crystallography for this project, that's why we include his name, I think. That's not my decision, probably. I think Dickerson suggested.

Hughes: Do you consider that work a big step? Because up until then, and correct me if I'm wrong, there was no evidence that synthetic DNA was actually biologically functional. Was that work the first demonstration?

Itakura: Yes, that is the first. Even [when] Khorana made gene for tRNA, he never clone, and he never show that functionality—after that, he showed of course—but before that he didn't show that that is biologically active. And lac operon was the first one—the synthetic DNA was cloned into bacteria and show the biological activity. So that is a big step.

Hughes: Did you have any feeling before you did this work about whether a synthetic gene would or would not be functional?

Itakura: I believe that it should be functional.

Hughes: Because the chemistry was accurate?

Itakura: Yes, the chemistry is accurate, and we knew that chemistry exactly following the sequence of lac operon. After removing all the protecting group, that should be the synthesized DNA which we would arrive to. So I have no doubt about it.

Hughes: Where did the lac operon come from?

Itakura: Bacteria.

Hughes: You put bacterial DNA back into bacteria so you wouldn't be worried about the species barrier?

Itakura: I don't worry about species barrier at all. We synthesized exactly the same natural product. So if you have chemically identical product to a natural one, that's biologically identical.

Hughes: But there are small differences. I don't know about the lac operon specifically, but isn't the lac operon in the bacterium a little bit different than the lac operon

in a human being? But not enough so that you would worry about whether it would function in a different species?

Itakura: Okay, species differences means the gene—For example, *E. coli* doesn't have an insulin gene. And we humans or mammalians will have insulin gene. So we put the human gene into bacteria, maybe not be functional. Yes, that's what many people argue.

Hughes: That was a worry when you got to somatostatin, right? Because you were working with a sheep gene and putting it into a bacterium? And the bacterium doesn't have a somatostatin gene?

Itakura: Okay, but the genetic code is universal. In mammalian system we using same genetic [code]—three letter of base code [for] one protein. And that system is exactly same in bacteria and human being.

Hughes: People were disputing whether you could turn bacteria into factories for human proteins, because of the species barrier. But you're saying you were a chemist, and if the chemistry was accurate, it shouldn't matter where the gene was working.

Itakura: Well, almost all molecular biologists say [it will] work. No molecular biologist says they worry about barrier between bacteria and—

Hughes: They wouldn't worry, or they would?

Itakura: As far as I know, Herb Boyer, Riggs, Ohno, never mentioned about that. They never expressed that kind of worry—because the genetic code is the same. Maybe control is different. The expression, making the DNA from RNA and then protein, that control mechanism is different.

Hughes: The next step is to discuss somatostatin. Should we leave that for tomorrow?

Itakura: Sure, that's fine with me. [laughs]

Hughes: You've had enough.

Itakura: That's enough, yes. [laughs]

[End Tape 2, Side A] ##

Interview 2: January 13, 2005
[Begin Tape 3, Side A]

Hughes: Art sent me a copy of the NIH application, which is dated February 1976, proposing to synthesize the gene for somatostatin. Do you remember whose idea it was to submit to NIH?

Itakura: Riggs, that's his idea. Yes, he said that we should do that to raise money.

Hughes: You probably wrote the part on the synthetic chemistry, and he wrote the rest? Is that the way it went?

Itakura: Yes.

Hughes: Then what happened?

Itakura: Score was probably very good, maybe borderline, and I heard some rumor before the official notice—probably funded. But unfortunately, the NIH turn down our application.

Hughes: Do you remember the reasons NIH gave for rejecting it?

Itakura: One reason is probably they don't believe we can make a gene within three years. I don't know other reasons, because I don't have the critiques. They usually send the critiques—actually, always they send the critiques.

Hughes: And they didn't in this case?

Itakura: Yes, they did, but I don't know, somehow I throw out.[laughs]

Hughes: You were probably disappointed.

Itakura: Yes, very disappointed.

Hughes: Did you ever learn who the reviewers were?

Itakura: No, usually that's a secret.

Hughes: But sometimes you hear through the grapevine.

Itakura: Yes. They tell us the people who were in the study section, so in some case twelve, sometimes sixteen scientists.

Hughes: Were they molecular biologists?

Itakura: I think in general medicine; that particular grant application went to that [section].

Goldsmith: I'm sorry; I just want to jump in. I just wanted to make sure that the history was accurate. I know based upon other things that both Dr. Riggs and Dr. Itakura said that the writing of the application was not simply divided—one person wrote one section, one person wrote the other—that it was more of a collaboration than that. While one may have focused more on [one section than] the other, I think they both were involved in writing the entire paper. I think Dr. Itakura can clarify that, but that's my recollection.

Itakura: Yes, I am expert of DNA synthesis, so my major contribution is chemistry. His major contribution is biology, and always we discuss the ideas, and then we mutually agree, what's the gene to synthesize and then start working. Obviously his English is much better than my English, so he's kind of what, a mentor or a leader of writing, and then we work together writing grant application.

Hughes: Getting back to the reviewers: this application went through medicine—is that what you were saying?

Itakura: General medicine.

Hughes: Was there a molecular biology section at that time?

Itakura: I don't remember a molecular biology section. I'm not sure.

Hughes: Well, the point I'm trying to make is it could be possible that the people that reviewed the application were not experts in the field, and didn't have a secure basis for judging whether this work was really doable in the time frame that you suggested.

Itakura: Well, okay, yes, probably they cannot judge the chemistry of the DNA synthesis. Because my application did not go to Khorana, so probably nobody could judge the overall capability.

Hughes: Yet they could have looked at the history, because I believe you told me yesterday that the lac operator synthesis you did in a year.

Itakura: Yes, actually shorter time.

Hughes: Well, you had a track record. Granted the somatostatin gene is not the lac operator, but still you had shown that it didn't take years and years and years to construct DNA.

Itakura: That's true. But we published lac operator paper in I think 1977.

Hughes: Oh, so it hadn't been published when the grant was being reviewed?[3]

Itakura: Not yet. Even published, we didn't mention how long it takes to making a gene. So probably nobody exactly know how long we take to synthesize a small gene.

Hughes: They may have known how long it took Khorana to synthesize the tRNA gene, right? It took him a lot of time.

Itakura: Yes, probably ninety-nine percent people don't know how long we take, but the people in the field knew that. I had learned from Dr. Narang—

Hughes: Yes, but the people in field weren't the ones doing the peer review, right? So are you saying that the experts in your field were not reviewing the NIH application?

Itakura: I have no idea of who review. But I'm sure that's not chemist.

Hughes: How do you remember the connection with Genentech beginning?

Itakura: Art—Dr. Riggs and I—tried to raise funds, actually mainly he was working on the fundraising, and we ask also Dr. Ohno, Levine, and somehow the City of Hope couldn't support. The answer was not straightforward. In other words, probably they would like to say no, but they didn't say no exactly.

Hughes: This is Dr. Ohno?

Itakura: No, Dr. Levine. Dr. Ohno and Levine, I think they went to the [City of Hope] Board of Directors, and their suggestion is, somehow raise the funds. Well, before 1975, Art has a relationship with Dr. Boyer. And then somehow Dr. Boyer met Mr. Swanson, he's the founder of Genentech, and they are also very much interested in funding a similar project. And so Art talked to Boyer, and that's the beginning of the connection between Genentech and City of Hope.

Hughes: Did you have any hesitation about accepting funds from a company?

Itakura: No. I guess no; I have no idea. I don't remember exactly what I thought.

Hughes: Well, was it common in biomedicine in those days to have corporate funding?

Itakura: At that time, right, it was very, very unusual because [biomedicine had] actually nothing to do for the production of some medicine or anything practical. Almost all, one hundred percent of molecular biologists working on the very, very basic science. Just like genetics of *E. coli* bacteria.

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3. The lac operator paper is dated October 28, 1976.

Hughes: Yes, no practical application.

Itakura: Not at all.

Hughes: But you don't remember thinking, "Oh, I'm not sure that I want to have a relationship with a company?"

Itakura: Well, as long as I stay here, it's okay. That's not so easy to remember, but unconsciously maybe I have some hesitation. I think I never expressed, so that's just my own thoughts. Very political answer.

Hughes: Before you began the experiments, how optimistic were you that indeed somatostatin could be expressed in *E. coli*?

Itakura: I'm very, very, very much optimistic. I have no doubt in my mind we are successful, so I am almost one hundred percent optimistic.

Hughes: And do you think Art was equally optimistic?

Itakura: Yes, he is also very optimistic.

Hughes: What were you basing your optimism on?

Itakura: Again, the genetic code of the *E. coli* and the human are same, and then what we are going to do is just changing the control of the expression, transcription and translation.

Hughes: Do you remember your first encounter with Bob Swanson?

Itakura: I believe we went to San Francisco and then met with Swanson and Boyer at the same time. I believe.

Hughes: At Swanson's office?

Itakura: I don't know if he has office or not.

Hughes: Well, he had an office. He was with Kleiner Perkins and had recently left. He had an office in the same suite in downtown San Francisco.

Itakura: Yes, central downtown.

Hughes: And was Tom Perkins there?

Itakura: First time?

Hughes: The first time, yes.

Itakura: I don't know; I don't remember.

Hughes: Do you remember what you first impressions of Swanson were?

Itakura: Just a businessman. [laughs]

Hughes: A *young* business man.

Itakura: A young business man, very enthusiastic.

Hughes: You didn't think there would be problems working with him?

Itakura: I didn't think of that. Well, when we carry out research we just ignore what he says; it doesn't help much.

Hughes: But there were slight problems. Do you remember that he wanted to go straight for insulin, rather than doing somatostatin first?

Itakura: At the beginning, yes, I have the same idea with him. When we discuss first time the actual plan, I'd made up mind already: I wished to start with insulin because insulin is more important. But scientific point of view, probably Art's is right—the somatostatin is his idea. He was asking Dr. Levine and other people probably, and the first step should be a small gene, not a big gene, in terms of relative size. Small gene we should start and engineer very quickly, and then establish that system. Then we can go into insulin. So I was not so much disappointed, but Swanson is probably very much disappointed.

Hughes: Art said this morning that Swanson resisted for quite some time. He really didn't want to do somatostatin first.

Itakura: Yes, he resisted.

Hughes: But were you convinced by Art fairly quickly that it made sense to go to somatostatin first?

Itakura: Yes, very quickly. Just ten minutes talking, and that's more than enough for me.

Hughes: So tell me the first scientific approach.

Itakura: Start in chemistry, or include everything?

Hughes: Yes, tell me the whole thing.

Itakura: I did not improve anything [in DNA synthesis] at City of Hope, because I have already improved every technique at the NRC in Canada. So I didn't do anything new, but just do the making of small oligonucleotide and then assemble into

DNA. So that part is nothing new. But maybe small improvement is just the purified oligonucleotide before cloning. That's all. Then first idea is to isolate the lac operator—[speaks Japanese to himself] yes, lac operator and the promoter—and then connecting through the synthetic DNA, then put back into the bacteria, and hopefully express the somatostatin gene.

Hughes: But it wasn't quite that easy.

Itakura: At the beginning, yes, we didn't see any activity of somatostatin, and the first trial was fail. But that always happened in the case of the molecular biology or chemistry, and usually successful rate is maybe ten percent or twenty percent. So of course we disappointed, but we had a plan B. [laughs] So we speculated probably that gene is transcribed and then translated, but probably product, somatostatin, is very small, only fourteen amino acids, and digested in bacteria. So we have to think about something to protect from digestion. And couple people have different idea: one is using protease minus *E. coli* strain. And the other one is come from Art, which [is to] attach the somatostatin gene at the end of the beta-galactosidase [gene], because the beta-galactosidase [is] a huge protein and very stable in bacteria. If you attach the somatostatin to the beta-galactosidase, the bacteria will produce fusion protein—a kind of hybrid—and then after purify the hybrid protein, then somatostatin could be cut off from the fusion protein.

Hughes: When you conceived this plan B, did you think a fusion protein would actually result?

Itakura: You mean the work—

Hughes: Before you had done the experiments, when you were still in the planning stage. I'm trying to find out how confident you were that these various approaches would work.

Itakura: The protecting idea I like very much, because in the chemistry we use always protection, protecting groups. So that's kind of a similar idea, but different concept. At that time Art was very confident, so I have no doubt about it.

Hughes: But you've got two minds that think very well chemically; if the two of you had not had chemistry backgrounds, it probably would never have happened, would it? Or at least not have happened in the way it happened?

Itakura: Probably not happen very quickly like that. So I still believe that chemistry is the most important, before I learn the molecular biology or biology. So I am very lucky that I have a chemistry background.

Hughes: And of course Art does too.

Itakura: Yes. His major was chemistry and molecular genetics.

Hughes: What about the possibility that the bacteria would degrade any somatostatin produced? Were you worrying about that before you actually did the experiments?

Itakura: Again, that was not my area, even at that time I didn't know that bacteria has a protease. [laughs] So again that's what Art indicated to me, and maybe a small peptide might be degraded—that's what he told me—but I don't know when he told me, but he told me that there is a way to overcome that kind of degradation.

Hughes: Do you remember the occasion when Swanson came down and you thought you had produced somatostatin, but you hadn't? Well, you produced it, as you learned later, but the bacteria had eaten it up.

Itakura: [laughs] After we show the result. The agreement between Genentech and UC San Francisco and City of Hope is they [UCSF] clone gene and also they express in the bacteria, and they going to send the extract to Art, and Art carry out the, I think, radioimmunoassay. At that time, when we have the result, and show Swanson the result, and nothing. So Swanson's of course very, very disappointed. That night we went to a Chinese restaurant with a few people, and then he has —I don't know—he may have a stomach flu or stomach problem, or maybe he ate a chili pepper, I don't remember. And then he stayed at Art's house, and then he had diarrhea and vomiting, so he went to the emergency [room], and he was quite sick.

Hughes: Maybe connected with the experimental results and maybe not.

Itakura: Yes, probably. Or just simply he had a flu.

Hughes: How did you feel when the bacteria were found not to be producing enough somatostatin to be detected?

Itakura: Well, kind of disappointed, but kind of expected. I get used to the experiment fail many, many times, so it was not the end of the world.

Hughes: Maybe that's a difference between a scientific outlook and Swanson's business outlook. I mean, he hadn't had the experience of science being more failures than successes, and you just carry on.

Itakura: Yes, I guess. Well, surprisingly, well not surprising—surprising for scientists—he has all kind of schedule: DNA synthesis finish such and such months; expression such such; and then fundraising, such such. He showed me that kind of a table, exactly scheduled, step by step. [laughs]

Hughes: What was your reaction to that?

Itakura: I said meaningless. I told him you never know when experiment works [or not].

Hughes: So Swanson thought that science could move on schedule.

Itakura: Yes. Hopefully.

Hughes: Oh, he hoped it could, yes.

Itakura: And then that's probably very important for him to raise fund.

Hughes: Yes, of course. The future of his company hung upon the results of the experiment. Did that put more pressure on you, because you knew that this company might fail?

Itakura: No, not at all.

Hughes: No? You just took the money and did the science?

Itakura: That's right. [laughter] I don't care about the business of it at that time. Right now, too. [laughs]

Hughes: Did you work pretty intensely?

Itakura: Yes, including Saturday. Start nine o'clock, and then maybe twelve hours sometimes, and I usually take day off on Sunday.

Hughes: Were you working harder on somatostatin than on other projects?

Itakura: I think I was hardest working when I was a graduate student. And postdoc, you have six days a week. And somatostatin, I have already at that time maybe four or five people, so was more busy on the supervising, check the experiments. So I think mentally, yes, very hard work, but physically not necessarily work harder than other project.

Hughes: And were you working just on somatostatin?

Itakura: At that time?

Hughes: Yes.

Itakura: Yes, no other project at that time. Oh, yes. A small project working with Dr. Dickerson I still have. I have a grant, and I maintain the lab at the Caltech, and I have one postdoc fellow. So he was working at the Caltech and collaborating with Dr. Dickerson.

Hughes: *E. coli* is not producing somatostatin, and so then you go to plan B, right?

Itakura: That's right.

Hughes: Do you remember what the time interval was between the failure and the success?

Itakura: I don't remember exactly. But that takes time, probably six months.

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

Hughes: [Tadaaki] Hirose was in your lab. What was he doing?

Itakura: He is a postdoc fellow, and I trained him. He's not DNA chemist—he's an organic chemist, but he has no experience of the DNA synthesis. So I train him couple months, and because his background is very good in organic chemistry, he could do it by himself very quickly.

He came to your lab to learn DNA synthesis? From Japan?Hughes:

Itakura: Yes. From Japan, yes. From Keio University.

Hughes: He was helping you synthesize the DNA?

Itakura: Yes.

Hughes: Were you doing it, too?

Itakura: Yes, I do it myself, too.

Hughes: And then sometime in 1977, Roberto Crea arrives. How did that happen?

Itakura: After he got the Ph.D., he went to Holland and trained by, I forgot his name, what his name? [Jacques Van Boom] [laughs] Trained by him for a couple years. I send a letter or he sent me a letter, I don't remember which way.

Hughes: I've seen those letters, and my memory is that you sent a letter to van Boom.

Itakura: Anyway, so I try to find the postdoc fellow for this somatostatin project. Then of course if we have trained person, we can do it very quickly for the project. And so I guess I ask him [van Boom] to find anybody who trained for DNA chemistry. And he told this Roberto Crea.

Hughes: Was Roberto using your triester method?

Itakura: His method learned in the Holland is different, and they just start in that phosphodiester method. So not familiar with the phosphotriester method. So I trained him maybe only just a few months, and he's okay.

Hughes: He came with the HPLC [high pressure liquid chromatography] apparatus, right? Or knowing how to use it? Did he actually bring the machine? No, you ordered it.

Itakura: Machine is too heavy to carry. [laughs]

Hughes: Yes. Was it his idea that you would have one?

Itakura: Yes. In his group they're using HPLC for the final purification of synthetic oligonucleotide.

Hughes: Was that a help?

Itakura: Yes, purification is much faster.

Hughes: Why hadn't you gotten one? No money?

Itakura: Yes, I had the money. No, I didn't use before HPLC, that's all. I think in Narang's group we were using very classical, slow method for the purification. That's the reason. I think there's no particular reason why we didn't use HPLC. I think we never use before.

Hughes: Let's see. [paper shuffling] Do you remember the occasion when you knew that the experiments worked?

Itakura: Yes.

Hughes: And what was it? Who was there?

Itakura: Art, and his technician.

Hughes: Louise [Shively]?

Itakura: Louise—maybe yes, maybe no, I'm not sure. I think Heyneker sent some samples to the lab, and then Art was checking the radioimmunoassay of somatostatin. Then we have about ten, maybe fifteen samples. Some samples are control, some ones are induction of the gene expression, some are not. Then we looking at the printout of the radioimmunoassay, and the printout show clearly that the gene is expressed and somatostatin is there.

Hughes: How did you feel at that point?

Itakura: I didn't feel at that time, not so much, actually.

Hughes: Why was that?

Itakura: I don't know why. [laughs] Because we expected it to work, that's one reason. The other reason is, I felt much better later. I don't know why. Not so much excited that time, yes. But later on excited; I was very excited.

Hughes: About somatostatin?

Itakura: Yes, somatostatin works.

Hughes: It began to sink in what it meant?

Itakura: I don't know that.

Hughes: Well, let me ask you, can you remember when you first learned about recombinant DNA? Would it have been before you arrived at City of Hope?

Itakura: Yes, actually [through] the journals, particularly *Nature*, *Science*; they publish the recombinant DNA review. Also of course the newspapers reported some kind of recombinant DNA approach.

Hughes: So it was familiar to you?

Itakura: I don't know familiar means, but at least I knew [of] some technique, technology.

Hughes: Had you ever thought of using it in connection with DNA synthesis?

Itakura: That's probably my major goal, using synthetic DNA for solving the biological problems. One is obviously cloning gene and produce the human peptide in bacteria. But that is a gradual learning process, so I can't tell you exactly how much I know at that time. It's very difficult to answer. But I feel, or maybe I smell, that small oligonucleotide is quite important to the study of molecular biology.

Hughes: Now it seems obvious that the two techniques would be mutually enhancing because, as you know better than anybody perhaps, maybe aside from Narang and Khorana, that it's a very tedious business doing DNA synthesis the diester way, and that you don't get very large amounts of DNA.

Itakura: That's correct.

Hughes: You were still very much a chemist, and the people working on recombinant DNA were more biologically oriented. So at least in the early stages, it was not

obvious that the two techniques coming out of different disciplines were going to be mutually enhancing, that they were going to work together.

Itakura: That's right. Yes, actually when I finish postdoc fellow[ship], I sent about ten letters to get a job, and I don't get good response from molecular biologists, except from the City of Hope and actually some interested company. But I'm not sure that interested company is much interested in the molecular biology or not. So the only institute I got the good response from is City of Hope. And [it was] because of Dr. Ohno and also Dr. Riggs. Probably they saw that the synthetic oligonucleotides are very important to molecular biology.

Hughes: Remind me what year was it that you sent out those letters?

Itakura: '73.

Hughes: '73. The first recombinant DNA paper isn't published until almost the end of that year, November 1973. It's happening that the two technologies are coming to fruition at more or less the same time.

Itakura: Yes, actually that's coincidence.

Hughes: Yes. It's also interesting that Dr. Riggs might be the linking figure. Correct me if I'm wrong—at that stage, your thought is mainly chemical. You're still very much a chemist—well, maybe a biochemist?

Itakura: No, actually chemist.

Hughes: Art's working in a medical research institute; everyday he's confronted with the fact that there are medical problems out there, and yet he's also got a strong chemical background. This is speculation on my part, but he seems to be the bridge figure who could think in both areas?

Itakura: I don't know he was working in the medical programs. He was working on the bacteria programs, I believe. He was one of the pioneer working on the mechanism of lac operon, how lac operon gene expression is [turned] on and off. He's an expert on that area. So I'm not sure he had any contact with medical research; I don't know of any…[trails off]

Hughes: I was meaning in a very general sense—the fact that City of Hope has a strong biomedical orientation, where you were in a chemistry group, were you not?

Itakura: Yes, I admit that once we start working at City of Hope, I feel always the medical problems. You have seminars, interaction with M.D., yes. There are so many medical problems, and particularly in this institute, diabetes and also cancer. In that sense, yes.

Hughes: I destroy my argument by remembering what you said yesterday, which was that you came out of pharmaceutical science; that's where your degrees are. Pharmacy and medicine are very close. So my argument's not very good. [laughs]

Itakura: Cure diseases by medicine. [laughs]

Hughes: Okay, let's see where we are now. What do you remember about the publicity that surrounded somatostatin? There was a press conference, wasn't there?

Itakura: Yes. I don't know—my feeling? Myself, just I feel I hate it!—Okay? [laughter]

Hughes: What part did you hate?

Itakura: No, not so much hate—a little bit disturbing. There's some people come into my lab asking questions and taking pictures with TV cameras. I felt disturbed, but maybe I took some advantage, so I should say that way.

Hughes: You didn't like the publicity, but in a way you did. [laughter]

Itakura: That's right; that's correct.

Hughes: Was there any discussion or any contention about the order of authors on the paper?

Itakura: Oh, yes, we had. Particularly Heyneker has a strong objection [that] I am the first author. Actually, he come to Los Angeles and we have one meeting, but—

Hughes: About the paper?

Itakura: About the paper and who is to be the first author. That's only [case] I know that somebody express unhappiness about the order of the authors.

Hughes: The first three authors are the DNA synthesis group—your group. Then there's Art, and then there's the San Francisco group, which of course is the cloning group.[4] The way I see Heyneker is that he was in Boyer's lab, and he was assigned the project. Boyer was the head of the lab; Heyneker was the hands. A pair of very good hands, and I'm sure not just hands but head as well, but the lab head nonetheless was Boyer. In your case you were kind of both: you were doing the work, but you were head of the lab. Is that your thinking about why you should be first author?

Itakura: No, that's not correct. The original idea of making the somatostatin gene and expression in bacteria is our idea, between Art Riggs and me. And that's one

4. See Itakura's curriculum vitae in the appendix.

strong point, and that was our contribution to this paper. If we don't have synthetic DNA, then we could not have published this paper as quick as this one, probably have to wait maybe one year or two years. So that's two arguments—that's my argument.

Hughes: What was Heyneker's argument?

Itakura: He said he did the major work. [laughter] Yes, that's probably true, but idea is all ours.

Hughes: You think that is true? That he did the major work?

Goldsmith: [interrupts] And by major you [Itakura] mean the greatest volume, not the most important.

Hughes: Oh, is that what you mean? Heyneker did more work, but not necessarily the most important?

Itakura: Not necessarily major work, but he did lots of work. The idea is ours, and in this paper, the synthetic DNA is one of the most—*the* important, the most important.

Hughes: So did he agree by the end of the meeting?

Itakura: Oh, I don't know. [laughter]

Hughes: Well, your name's on the paper as first author!

Itakura: I think he [Heyneker] decided really—Probably Art—well, not particularly Art; particularly Boyer probably convinced him.

Hughes: Well, you were dealing with a lot of very energetic, competitive people.

Itakura: Yes, that's true. [laughter]

Hughes: I think probably Art and Herb were the only ones going to calm things down. I imagine that Crea could be pretty competitive as well.

Itakura: Oh, no. In that case, not necessarily. He's very competitive, yes.

Hughes: He'd come in at the end of the experiments, hadn't he?

Itakura: Yes, but the major contribution of DNA synthesis from myself, actually.

Hughes: That's what I'm meaning, that Crea—how to put it?—he wasn't there for most of the work.

Itakura: At the beginning, yes, that's true.

Hughes: Who made the decision to publish in *Science*?

Itakura: I think Boyer—I believe Boyer.

Hughes: There was no problem getting the paper accepted?

Itakura: No problem, because he talked to senior editor. When we are writing the manuscript, he talked to senior editor, the editor-in-chief. I don't remember his name.

Hughes Herb knew him?

Itakura: Yes.

Hughes: Do you remember repercussions from your scientific colleagues?

Itakura: Yes, very much excited, because they'd never seen the TV cameras. [laughter] Visitors. So it's very much exciting, and everybody very happy at that time, yes.

Hughes: The story of the somatostatin success was announced in a [U.S.] Senate subcommittee by Philip Handler, with the recombinant DNA controversy going on.

Itakura: Yes.

Hughes: Do you have anything in particular to say?

Itakura: At that time I didn't know. I heard that the United States spending maybe two hundred, three hundred million [dollars] every year for the genetic and molecular study—the molecular biology study of bacteria. Congressmen argue that we are wasting—

Hughes: Wasting money.

Itakura: So probably this is one example. The first example, we are doing very good basic research to lead to this kind of [applied] research. So that I remember.

Hughes: Did you as a chemist have much awareness of the recombinant DNA controversy that was going on at the same time?

Itakura: Yes, of course it was almost every day in the newspaper, and also the journals of course.

Hughes: What did you think?

Itakura: That's probably—nothing. [laughter] Just afraid if something happen. But I believe that [recombinant DNA] probably completely safe, because always happen that recombination between two species, or between bacteria and in some cases human, I thought that probably shouldn't be afraid of anything. We were joking that maybe if we can't do any recombinant work, maybe we should do it in a garage or something like this. Well, one argument [was] that we particularly using DNA from the chemistry, not from the natural sources. But, nothing.

Hughes: So it wasn't a major issue as far as you were concerned in conducting the experiments?

Itakura: Not at all.

Hughes: Were you involved in any way with setting up the contract between City of Hope and Genentech?

Itakura: I think almost none, but I went to one meeting, and at that meeting is [with] Swanson. I think Swanson and somebody else came; I have no idea [who]; I don't remember. Then they [Swanson and the other Genentech representative] propose to City of Hope we provide such such money and so on and so forth. Then I believe Art talking about the scientific part, and that's the only meeting I was involved. Oh, tried to get the approval from [City of Hope] board of directors. That's why Swanson—I don't remember other person—came and then present their plan, and present our plan, that's [all] I remember, and any other cases I was not involved in.

Hughes: Well, do you remember what the action of the board of directors was?

Itakura: That's approved immediately.

Hughes: They didn't see any problem?

Itakura: No problem, as far as I know; I didn’t hear anything.

Hughes: You began to help to write the patent at about that same time?

Itakura: Not the same time, after finished the project.

Hughes: Yes, of course it would be.

Itakura: And before the publication of the paper in the *Science.* What his name, Tom—?

Hughes: Kiley.

Itakura: Tom Kiley, yes. How many times we went his place? Maybe a couple times, I don't know.

Hughes: He at that time was at Lyon and Lyon, right? He was in Los Angeles?

Itakura: Yes, Los Angeles. And he's a very smart guy. I think he taught himself the molecular biology, and he wrote almost all patent by himself. I believe maybe once, maybe twice, I went to his office and read patent application. Yes, that's all I remember.

Hughes: Patenting at that time was much more common in chemistry than it was in biology.

Itakura: Yes, that's correct.

Hughes: So did you come with some understanding of intellectual property law?

Itakura: No, not understand it at all. [laughs]

Hughes: But it wasn't a strange idea to you, to patent?

Itakura: Strange idea—no, not necessary strange idea. It's okay. At least I know what the patent means. If there's something invented and useful, yes, protect the right. I knew that even at that time.

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

Hughes: The approach that biomedical people have towards intellectual property now is very sophisticated; they know that as soon as they have an invention that they should contact an attorney. But that, to my knowledge, was not true in the mid-seventies; it was not an obvious thing for a biologist to think about intellectual property. But it was more common in the physical sciences, right?

Itakura: Chemistry, yes. If you invent a new compound, and it has a pharmaceutical activity, yes.

Hughes: Were you ever aware at that time of any criticism of taking out a patent on your work?

Itakura: Criticism? To get the patent? No, I don't think so. No, I don't remember any.

Hughes: Of course the intention of patenting is to make commercialization possible, or more possible. To critics of recombinant DNA, that meant that the field was expanding into industry. Hence patenting to them was a bad thing when it came to anything involving recombinant DNA or DNA in general.

Itakura: Oh, okay.

Hughes: For example, when the Cohen-Boyer patents were being applied for, both Boyer and Cohen had to contend with critics. You don't remember anything like that happening to you?

Itakura: Not to me directly, no, but maybe to other people. I have no idea.

Hughes: Did Swanson offer you Genentech stock?

Itakura: Yes.

Hughes: And did you know what that meant?

Itakura: No, [laughter] at that time probably just a paper.

Hughes: That's apparently what a lot of people thought, including Richard Scheller. [laughter]

Itakura: I know that. Even though we successful when we detected somatostatin in bacteria, I didn't think that this is going to be commercially useful. But we happy to know the human gene express in the bacteria. So that's all.

Hughes: Yes, you were thinking of the science. When did it become obvious to you that this company might be a commercial success?

Itakura: After we successful to produce the insulin. And then in 1982, '83, I don't know, '84, at that time some first royalty come from Genentech to City of Hope.

Hughes: And then you began to realize that there was something profitable here. But you never could have conceived how profitable, right?

Itakura: No, no idea at all.

Hughes: Anything more that you wish to say about somatostatin?

Itakura: Somatostatin? Not the science, but patent application. Tom Kiley is very impressive because he writing the patent application maybe within ten days, probably two weeks, and he doesn't have any knowledge of molecular biology at the starting point, and he finish very quickly, and hard working and very smart guy.

Hughes: Is the first patent a method patent?

Itakura: I think all patent is a method.

Hughes: There were product patents as well.

Goldsmith: I think all the Riggs-Itakura patents were method patents. Genentech may have some product patents, but all the Riggs-Itakura patents of significance are methods.

Itakura: So I respect the lawyer. [laughter] Many lawyers are hard working, very smart. I realized the first time with that one [Kiley], and of course business guys are hard working, very smart.

Hughes: Like scientists.

Goldsmith: Scientists are far smarter than we are.

Hughes: Well, we'll not get into that one. All right, human insulin. You had said how for some time you had thought that should be the goal, and how you were persuaded by Art to try the somatostatin first. With the resounding success of somatostatin, of course insulin became the next thing to do right? I mean, it was obvious.

Itakura: Yes. That's very obvious.

Hughes: But was it obvious to you that you were getting into an incredible race, that the competition was fierce to clone and express—the rat insulin gene had been cloned already; I don't know if it had been expressed.

Itakura: No.

Hughes: But anyway, it was a hot race. Were you aware that there were competing groups at UCSF and at Harvard?

Itakura: Yes. I knew at that time, yes.

Hughes: Did you like the fact that it was a race?

Itakura: Well, I don't know I like that—we just do our job as soon as possible. And I remember [Howard] Goodman at UC San Francisco already cloned that cDNA for insulin gene.

Hughes: It was rat insulin, wasn't it?

Itakura: I think that's rat, yes. Also the Harvard group tried to clone human insulin gene, but that probably out of race. At that time probably we knew that—did we know that?—the gene is made of not only the straight continuous gene, and there is a gap we call intron between DNA-coding peptide. Even if they isolate human insulin gene, that's not so easy to make the DNA in expressible form in bacteria.

Hughes: You're talking about the A and B chain?

Itakura: No, the gene is usually made of exons which encode peptide, and introns which is between exon.

Hughes: Tell me your point again.

Itakura: In the bacteria, any gene is continuous coding the peptides—

Hughes: No introns.

Itakura: But in the human gene or a mammalian gene whatever, always discontinuous.

Hughes: And that was just becoming known?

Itakura: Maybe yes, maybe no, that's maybe confusing.

Hughes: The discovery [of introns] is right around that time.

Itakura: Around that time, yes.

Hughes: By lly Gilbert's group, right? What difference did that make to you?

Itakura: Nothing for us. As I said, just we should finish as soon as possible the DNA synthesis. So it's a race, but I don't have so much pressure.

Hughes: You were just going as fast as you normally went?

Itakura: Yes, that's right.

Hughes: But according to Art Riggs, you had Swanson—

Itakura: Ah, Swanson! [laughs]

Hughes: —pushing, pushing, pushing.

Itakura: Yes, there is some personal difference between scientists and business people.

Goldsmith: I think one thing you should know: Keiichi is being modest. I think that Keiichi was viewed as perhaps the fastest person in the world at what he did. He was the fastest gun in the West, so—

Hughes: He didn't need to be speeded up.

Goldsmith: He was already faster than anybody else.

Hughes: How was Swanson pressuring you? Was he coming down here every once in a while?

Itakura: Yes, actually many, many times, and have lunch or have dinner, or sometimes play tennis with him. But I don't know, maybe I'm ignorant, I don't know exactly I feel pressure from him or not.

Hughes: You were just doing your science.

Itakura: Yes, and whenever we finish, finish.

Hughes: Well, Art said—he didn't think he expressed it to Swanson—that he did find it a little irritating to have—

Itakura: Yes, always. Swanson has lots of pressure, that's no doubt about.

Hughes: Whose idea was it—or was it obvious that the A and B chains had to be synthesized separately?

Itakura: Actually, the insulin is made of precursor, B-C-A; that's all of the gene. And then in pancreas, C [C-chain] is removed, and then [the remainder] becomes your insulin. With C included, we call it proinsulin. After removing C, that is the insulin. So C-chain is essential to form the chemical structure between B and A, and bacteria cannot remove the C-chain. But chemically we can make the insulin from B-chain to A-chain. So that's why we start making A-chain gene, B-chain gene, express separately, and then make the B-chain protein, A-chain protein, and then chemically combine and produce insulin. That's the whole idea.

Hughes: Does that relate to the mini-C project?

Itakura: Yes, that's kind of the idea I have. Instead of making the C-chain, which is in a human case about thirty amino acids, maybe we can make smaller, maybe ten or so, and then save the DNA synthesis. Because if we have ten amino acids, we can make only thirty-base DNA. But that idea didn’t work, unfortunately. We don't know the reason.

Hughes: To this day you don’t know the reason?

Itakura: Right. And later on, Genentech synthesized the C-chain. Now the other reason why we didn't go to C-chain approach first is we didn't know the enzyme to cut off the C peptide. Well, we know the presence of the enzyme to cut off C peptide in the pancreas, but we don't know exactly what kind of enzyme to cut, and nobody know how to purify that enzymes. So just make first B-chain, A-chain approach.

Hughes: You had trouble with the B-chain?

Itakura: Some, yes, we had a mistake. At that time the way we making the oligonucleotide is units of three bases. And the one guy made a mistake and put the wrong three bases during synthesis, so we got the wrong sequence. After cloning we found it, and then we correct it and get right gene.

Hughes: And about how long did it take to correct it?

Itakura: I don't know, maybe two months?

Hughes: You had to start the synthesis all over again?

Itakura: No, just one problem.

Hughes: Yes, that one piece. Was that the only problem in the insulin work?

Itakura: Yes, the approach is itself identical. I mean, its chemistry and molecular biology is exactly the same as somatostatin, so we didn't have any problem as far as I know. Maybe Genentech they might have a problem.

Hughes: Do you remember that there were two times when people from Genentech came down to work at City of Hope? The first time was with Heyneker and Goeddel, right?

Itakura: I think Goeddel—

Hughes: Do you remember what exactly they were doing? They weren't doing any DNA synthesis because you were doing that.

Itakura: Yes. They would like to assemble the small DNA fragment we synthesize to the assembly of the large DNA gene, in other words, ligating the small fragment together. And yes, they stay in motel nearby, and they working very hard, particularly Goeddel is crazy hard worker.

Hughes: Even harder than you?

Itakura: I don't work more than twelve hours, and he works maybe twenty hours. I think he stayed two weeks, and then everyday working crazy.

Hughes: And then the second time he came down, but this time with Dennis Kleid, and it was sort of the same pattern, crazy?

Itakura: Yes, crazy. [laughter] Hard working.

Hughes: What did you think of them as scientists?

Itakura: Goeddel? Goeddel is particularly very good science, that's no doubt about. He was a leader of the Genentech science. Probably without him probably Genentech was not successful.

Hughes: You think? That much?

Itakura: Probably the most important person. Used to be. But now Scheller is very important. But the basis of the Genentech was established by Goeddel.

Hughes: Yes, well, he was certainly the cloner, wasn't he? He cloned one gene after another.

Itakura: Yes, cloner.

Hughes: Have we covered human insulin?

Itakura: Yes, after the human insulin, then move onto the human growth hormone.

Hughes: It was a pretty seamless move? I mean, one project led right into another?

Itakura: Yes, probably no problems. The human growth hormone is about one hundred ninety amino acid, and quite big gene compared to the human insulin. So to me if we synthesize all chemically the DNA, it's a big challenge, and very good establishment. So I propose making the DNA for human growth hormone. But a Genentech scientist, I believe Goeddel, they propose the hybrid approach or fusion approach, using the cDNA—part of the gene should be cDNA and part of the gene made by DNA chemistry.

Hughes: That was Goeddel's idea?

Itakura: Well , I don't know if it was that idea.

Hughes: But it wasn't your idea?

Itakura: Not my idea. My idea is just making straight from just the whole gene.

Hughes: And you were really willing to put in that kind of work?

Itakura: Yes, I believe that we could do it very quickly. Anyway, somehow they got the human growth hormone cDNA.

Hughes: Well, they got it from [Peter] Seeburg.

Itakura: Yes, I guess so, that's all the big trouble. [laughs]

Goldsmith: There's apparently controversy over that.

Hughes: Well, I'm not going to get into whether he took the clones from UCSF or not. Goeddel swears that he used his own clones, you know. But it is true that Seeburg came from UCSF to work at Genentech, and he came at the turn of 1977?

Itakura: Yes. That's a big surprise actually because they don't like the businessmen particularly.

Hughes: Seeburg and [Axel] Ullrich?

Itakura: They say that they don't like businessmen, so that's a big surprise. But anyway, they work a few years for Genentech.

Hughes: Well, there were reasons for them to leave UCSF.

Itakura: Ah, okay. Well, I didn't know why they left UC San Francisco.

Hughes: Yes, it's a very controversial period of history. [laughs] So, you must have had to deal with Seeburg, right, because he was supposed to be Genentech's growth hormone man?

Itakura: But maybe only I met him a couple times, that's it. Because we just synthesized the amino acid from first amino acid to twenty-first or twenty-second, and we just make that DNA.

Hughes: Now, were you okay with that? You implied that you wanted to synthesize the whole gene.

Itakura: That, in the chemical sense, not okay. But conceptually that's okay because once we were very successful in making somatostatin in bacteria, and then we prove we could make insulin in bacteria, and what else we can do that doesn't matter too much regarding the concept. But in a chemical sense, maybe we could challenge the making of DNA for the whole gene. Yes, that's a little bit disappointing. I don't know. We could argue? I didn't argue so much at that time, yes. But always we need more money, and Swanson doesn't want to spend too much money, so that's it.

Hughes: That was a cost saving measure as far as Genentech was concerned?

Itakura: That's right, yes.

Hughes: I was going to say it was the beginning of Genentech's in-house research, but that's not true because they had their insulin team as we've discussed.

Itakura: Yes, insulin is at City of Hope, and—

Hughes: Both institutions are working on it. Did it go pretty smoothly, the human growth hormone research?

Itakura: Well, I don't know what is going inside Genentech, but our part is—Ah, we had one problem, I don't know big problem or small problem. The one guy working with me I think refused to give small oligonucleotide, the part of the human growth hormone, to Genentech. Some miscommunication between that guy and Swanson. The guy working with me insist they should give stock to that guy when they finish the DNA synthesis [because] that's what Mr. Swanson said. The guy working with me told me that story, and Swanson said, no, he never said [he would give stock to him]. So I have no idea which is right, but we have some problem maybe one month, two months, he refused to give up that oligonucleotide, so that's only one problem we have.

Hughes: But eventually he did?

Itakura: Yes.

Hughes: So that slowed down the growth hormone project?

Itakura: Yes, a little bit slow down.

Hughes: I am a little bit confused about the patents. Did the first patent cover human growth hormone as well?

Goldsmith: Yes, it does. It was a broad method for expressing human proteins in bacteria.

Hughes: So you didn't have to write another patent?

Goldsmith: No. As I said, I believe in the making of the growth hormone gene, Genentech may have had some techniques that they developed in making growth hormone that might be growth hormone specific. But the original patents cover the expression of human proteins in bacteria.

Hughes: Right. You didn't have anything to do with the development, did you? That was all handled by Genentech [and Eli Lilly] or, in the case of growth hormone, KabiGen.

Itakura: Yes, I didn't do anything.

Hughes: So you synthesized the DNA, and then—

Itakura: That's all.

Hughes: In fact, City of Hope was out of it, wasn't it, because Art didn't do any more either?

Itakura: Yes, that's right.

Hughes: Genentech does some development, and then it's turned over in the case of growth hormone to KabiGen.

Goldsmith: And [Eli] Lilly develops?

Itakura: And Lilly develops [insulin].

Goldsmith: Right, because Genentech didn't have the facilities to make either of those products commercially at the time.

Hughes: Do you remember that again there was a competition, and again you were in competition with the UCSF group, on growth hormone. [John] Baxter's group—Seeburg had been in Baxter's group at UCSF—got wind that Genentech was going to make an announcement about human growth hormone and rushed out an announcement on the same day or the next day. Do you remember that City of Hope/Genentech and UCSF were in a tight race for growth hormone as well?

Itakura: I thought that that's not a tight race. Because we, after finish and write the patent and also send the paper to *Nature*—

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

Itakura: —*Science* paper, somatostatin; and the *PNAS* [*Proceedings of the National Academy of Sciences*], insulin; and the growth hormone, *Nature*. I think we are very careful; we didn't make any announcement before publication. So I believe, after we get the notice from *Nature* of acceptance of the paper and then publication date, we announce. I believe that was it. I'm not sure, but I believe that way.

Hughes: Well, it seemed to me that UCSF claimed to have published before Genentech, but I think it was—what do you call it when you write a preliminary paper?

Itakura: Letter.

Hughes: Yes, it was a letter.

Itakura: But that's probably only cloning, not the expression—

Hughes: Yes, it is cloning.

Goldsmith: The expression was done with somatostatin.

Hughes: Well, my notes say it was cloning and expression, but it's [expression of the] human growth hormone cDNA, of course.

Itakura: cDNA expression.

Hughes: And that letter was published August 10th, 1979. My notes say the Genentech/ City of Hope paper was published in October 18, '79 and described expression of human growth hormone.[5] UCSF had made an uncleavable fusion protein.

Itakura: Ah, okay, yes. That's probably right.

Hughes: So if you're talking about cloning and expression, then Genentech is first.

Itakura: But that was not medically useful.

Hughes: The fusion?

Itakura: Fusion protein.

Hughes: Right.

Itakura: So patent? I don't know, that expression is probably not useful, and then maybe they cannot get a patent for the expression of the fusion protein. I don't know. I have no idea.

Hughes: They certainly filed patents, but I don't know what happened.

Itakura: Okay, now I remember, yes.

Goldsmith: The original somatostatin patent is very, very broad and covers most expressions of proteins in bacteria. So while other folks may have been able to clone certain genes, for the genes to be useful you had to use the Riggs-Itakura method to express them.

Hughes: Yes, as I remember the following patents are more specific. They're about cloning and expressing a specific gene, [Goldsmith talks in background.] But I'm not up on this.

Goldsmith: The Riggs-Itakura patents are considered pioneering patents, which are a block of patents that people might be able to build on but they still have to use the fundamental technology.

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5. See reference in Itakura's curriculum vitae.

Hughes: Well, I've heard Tom Kiley call the Riggs-Itakura patents the commercial or industrial counterpart of the Cohen-Boyer recombinant DNA patents, which of course were on the basic science.

Goldsmith: Right, they're very, very broad.

Hughes: Well, that's about all I have to ask. What would you like to add?

Goldsmith: For history.

Hughes: For history.

Itakura: Nothing particularly. At least at the beginning, we just interested in science and just tried to prove that synthetic DNA is functional. That means transcribe and translate it in the bacteria, and any DNA can be expressed in the bacteria. That was the original goal. To me at the beginning, I didn't think about any commercialization, or we could make the commercially useful peptides, like insulin or growth hormone. But [the] technology surprisingly works. We didn't know that kind of technology [of] large scale production, [if] the fermentation of large amount of bacteria, for example, 10,000 liter, is possible, and then produce large amounts of peptide—it's beyond my scope. So, I didn't think that maybe our technology was very useful for commercial purpose. But actually Genentech proved I'm wrong, and then they produce large amount of the peptide in bacteria. And that's very useful for the treatment of diabetes patient, and also they produce human growth hormone for the treatment of the short stature people. So I'm very happy to at least contribute some of the—solve the medical problems. That was my long-time original goal when I start my PhD in the pharmaceutical school. So I'm very happy with the project, and I work with many nice people. At least I come to California and I like many people, almost all people, and I don't hate anybody. And so, what else? I'm happy, working with those people.

Hughes: Did you ever consider forming a company of your own or joining a company?

Itakura: Not at all. I'm very happy, pretty happy, that I'm working here, City of Hope, on sometimes basic research and sometimes applied research, and very comfortable. The City of Hope leave me alone, whatever I can do, and fortunately I have the royalty income, and I can do whatever I'd like to do.

Hughes: Very nice ending. [laughs] Well, not an ending—

Itakura: Not yet ending.

Hughes: —you're not through. An ending of the interview.

Itakura: Hopefully I can do something different and exciting research in the future.

Hughes: Do you have ideas?

Itakura: We working on the relationship between obesity and cancer.

Hughes: That's a hot field.

Itakura: Yes. They are very similar, cancer and obesity. They accumulate the fatty acid in the cells; that's very important for cancer cells to survive and grow. Of course the obesity is accumulate fat in the adipocyte, fatty cell. So I just wonder, why cancer is doing same thing as fat cells? So that's my goal to resolve—why? And working on the mechanism. Hopefully work out before I retire.

Hughes: But no firm dates about retirement?

Itakura: No. [laughs]

Hughes: Depends on how the research goes, probably.

Itakura: Ah, probably yes.

Hughes: Well, I thank you. It's been a pleasure.

[End Tape 4, Side B] ##
[End of Interview]

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EXPERIENCE

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HONORS AND AWARDS

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1979 Gallery of Medical and Scientific Achievement - City of Hope National Medical Center

PROFESSIONAL MEMBERSHIPS

American Association for the Advancement of Science

CURRENT EDITORAL BOARDS

1980 - PresentDNA and Cell Biology

PATENTS

Patent Number: 4,356,270Recombinant DNA cloning vehicle
Patent Number: 4,373,071Solid-phase synthesis of polynucleotides
Patent Number: 4,401,796Solid-phase synthesis of polynucleotides
Patent Number: 4,571,421Mammalian gene for microbial expression
Patent Number: 4,598,049General purpose gene synthesizer
Patent Number: 4,704,362Recombinant cloning vehicle microbial polypeptide expression
Patent Number: 5,221,619Method and means for microbial polypeptide expression
Patent Number: 5,583,013Method and means for microbial polypeptide expression
Patent Number: 5,750,380DNA polymerase mediated synthesis of double stranded nucleic acids

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