This is an oral history interview with Dr. Flossie Wong-Staal on the National Institutes of Health's response to AIDS. The interview was conducted at the National Institutes of Health on 10 December 1997. The interviewers are Dr. Victoria Harden, Director, NIH Historical Office, and Dr. Caroline Hannaway, Historical Contractor, NIH.

Harden: Dr. Wong-Staal, we'd like to start by talking about your personal background and education. You were born in China, and your family moved to Hong Kong in 1952, where you attended an all-girls' school. Can you tell us about your family, your father, your mother, and your education prior to going to college?

Wong-Staal: Yeah. I grew up in a family of four children, two boys and two girls. My father was, is in the import-export business. My mother was a housewife. She did not attend college. She stopped at the high school level. Among my brothers and sisters, I'm really the only one who went to college. So people often ask me whether I have a role model in my family, and, actually, I can't really say there is a role model. But, on the other hand, my parents have been very supportive of my pursuing my education. They've never, you know, had the concept that girls should not be, have higher education, and, on the contrary, they were very happy and pleased and proud of my accomplishments. And I think in part, you know, I always think that my mother is very intelligent, and she probably was frustrated that she never had the opportunity to have a career, and she was happy to sort of see me having the opportunity.

Harden: Where did you come in the birth order?

Wong-Staal: I was the third.

Harden: You were the third?

Wong-Staal: Yeah.

Harden: Were you interested in science as a child?

Wong-Staal: I was interested in a whole range of things. But I was also interested in literature and poetry and novels and so on. But the way the high school system is in Hong Kong is that you have to choose to go into science or non-science, really, early on in high school, I guess starting from high school, you know, after junior high. But, so, part of the mentality is that if you're smart, you should go into science. So it's almost like, you know, you're told that you should go into science. And people are usually accept that because they feel it's an honor and a privilege. So I can say that it's almost by default that I was _____ in the science path. But I, of course, never regretted it. I enjoy science, and I'm very happy with what I'm doing.

Hannaway: So the high school was on the British model.

Wong-Staal: Right, exactly, yes.

Hannaway: And was it an English-speaking high school that you went to?

Wong-Staal: Yes. The high school--it was actually run by American nuns, but the system in Hong Kong is the British system.

Hannaway: My sister and brother-in-law lived in Hong Kong for many years, so I know a little bit about the schooling system.

Wong-Staal: Right, right, yeah.

Hannaway: Why did you decide to move to America rather than Britain for your college education?

Wong-Staal: It was sort of arbitrary, I think. I also applied to Canada _____. But I had friends or classmates who were coming to America, and specifically going to UCLA, where I ended. So it was part of the desire of being with people I know that made that choice. And the other thing I think is that, just for people in Hong Kong, they're more familiar with, I think, through the television, movies, whatever, you're more familiar with--the West Coast in America is more familiar.

Hannaway: Was there a particular person or instance that influenced you to study bacteriology as an undergraduate?

Wong-Staal: Not any particular person. I was interested in biology as a whole, but I think microbiology, bacteriology, was of particular interest to me. I just, you know, like the subject.

Hannaway: There was not a teacher or a specific person.

Wong-Staal: Not anyone particularly that inspired me. But I have to say that I had very good teachers at UCLA for those courses.

Harden: Would you comment a little bit on your graduate training. Were there professors at that level who influenced you particularly?

Wong-Staal: I think at the time when I chose molecular biology because that was an era when there were a lot of exciting things happening, and I think there was cloning discovered with the restriction enzymes, so things are just

becoming possible. And I think also the oncogenic viruses and the reverse transcriptases also around that time, maybe a little bit later, but close to that time. So it was a very exciting field. I mean, it was sort of what physics was like a decade before.

So I--even though at that time, you know, I remember there was an article by Gunther Stent published somewhere, "The Rise and Fall of Molecular Biology." He thought that it was the peak of molecular biology, but then, from then on, it could only go downhill. But, of course, that was very premature. So I think it was, I mean, again, the right choice, but at the time I think a lot of people in my generation or in my peer group seemed to choose that direction.

In terms of my professor, my thesis professor, he's an older, in fact, an older botanist, but that then became, turned into a molecular biologist. He was very nurturing, although he is sort of like the grandfather type. But overall, it's a very good experience because of his attitude, and caring attitude, towards his graduate students. And had good interaction because UCLA, the molecular biology was not a department. It was an intradepartmental institute. So we actually got to interact with people in chemistry and in microbiology and so on. So it was a very positive experience.

Harden: What was the name of your thesis advisor?

Wong-Staal: Sam Wildman. Again, you know, as I said, he's an older person who worked mostly on tobacco, _____ TMV _____ virus, but also the tobacco

plant, fraction 1 protein, which is an enzyme, carboxydismutase, which turned out to be very important.

Hannaway: Did you ever think of going to medical school, or you were always focused on being a Ph.D. research scientist.

Wong-Staal: I think I had an aversion to the blood and guts of medicine. I mean, I like the biochemistry, molecular biology approach. But I don't think I could have gone through all the medical training.

Harden: And you've never changed your mind since.

Wong-Staal: No. It's better to work with M.D.s rather than to be an M.D.

Harden: I want to come back to the excitement of molecular biology in the early '70s, because you arrived at the NIH in 1973, and so you were right there as all these new things...

Wong-Staal: Right.

Harden: In thinking back in terms of what we know now and what was known then and how exciting it was to be learning these new things, are there particular things that stick in your mind as being just the most exciting kinds of things that you remember personally that really impressed you?

Wong-Staal: I think really the cloning aspect, the ability to purify genes and to amplify them enough to study every detail was something that wasn't possible before.

Harden: You saw that as something that would be...

Wong-Staal: Revolutionary and open up all kinds of possibilities. And, of course, now there's so many new technologies that have developed, and we always

thought that if we can use the techniques we have now to go back to our thesis, we could have done so much more, you know.

Harden: When you arrived at the NIH in '73, you were a Fogarty fellow. First, several questions. What led you to come to the NIH at that point?

Wong-Staal: Well, at that point, I think it was partly personal, because my husband was assigned to NIH, so--and I just was married for a year or a couple of years then, so that was the clear necessity. But also, there are several labs at NIH that have interests that match mine, so... For example, I mean, one of them, of course, is Gallo's lab, because of the idea to go after human retrovirus. At that time, the studies on animal retroviruses was in full swing, and I think, again, there's a lot of excitement with the oncogenes and so on, of retroviruses. So I think that was a very attractive area to get into.

Harden: So you all were able to arrange a dual appointment when you came. Your husband had an appointment and you had an appointment simultaneously.

Wong-Staal: Right. He had an appointment first, and then I started applying, I think, to a few labs, and then I ended up...

Harden: As a Fogarty fellow, does that imply that you were not a U.S. citizen at that time?

Wong-Staal: At that time, I was not. I came from Hong Kong, so I... I was married, as I said, a couple of years to an American citizen, but it takes five years before you can become a citizen, so I was still in transition.

Harden: When did you become one, just for the record?

Wong-Staal: Well, I think it was 1976.

Harden: Nineteen seventy-six.

Wong-Staal: Yeah.

Harden: Now, which laboratory were you in when you first came to the NIH, and what did you do for your first research project?

Wong-Staal: I came to Bob Gallo's lab, and initially I was working on different things. One is intracisternal A-particles, you know, how they replicate, you know, the biochemical analysis of intracisternal A particles. And the other is, at that time, David Gillespie was a section chief within the lab, and he's the person who actually innovated the hybridization procedure with Sol Spiegelman. So I was trained with him to learn some of these molecular techniques, hybridization.

Hannaway: You decided, as we know, to stay at the NIH, and then you had positions as visiting associate and cancer expert. Can you tell us what made you decide to stay, and would you comment on the environment for young researchers in the intramural program at that time.

Wong-Staal: I think NIH is a wonderful place to build a career, because, you know, you don't have to write grants and you don't have the teaching obligations, and it's a lot of opportunities for interaction. And it's also where the center, sort of the mecca. The people come and give seminars. So it's a very exciting place. And it's hard to really find comparable environment outside, I mean, especially in a period when you want to have the maximum productivity, because every move really means downtime, you

know, at critical points in one's career. So I think once you're at NIH, often there is a great inertia to leave NIH just because you're used to all these privileges. But at the same time, at some point, I guess, it's good to have the change.

Hannaway: You can decide that your later career. We'll come to that later. Could you just make a comment about whether the NIH was receptive to female researchers at that time? Or did you feel it was perhaps somewhat of an old boys' club or young boys' club?

Wong-Staal: Actually, I personally, throughout my career, have not experienced any overt discrimination on the basis of being a female or on the basis of being a foreigner. I mean, sometimes it's hard to dissociate these two minority standings. But, obviously, I see it happening, and sometimes it's real subtle. It could be at the higher level, you know, high-level decision-making, and that's when the old boys' club operates. But when you're young and starting, I think I don't see too much discrimination.

Hannaway: In 1978, you became a senior investigator in the laboratory of tumor cell biology at the National Cancer Institute. Can you tell us a bit about the research you were focusing on in the period before the advent of AIDS?

Wong-Staal: Yes. We were looking at using, looking at the primate retroviruses, particularly the gibbon ape leukemia virus and some of the animal transforming viruses, simian sarcoma virus, AMV, and so on, so, to look at them as models for eventual application to the human system. The monkey virus, of course, is very relevant because they are exogenous

viruses that cause disease and horizontally transmitted. And then the oncogenes, because they're _____ genes, we were interested in whether they may, or the expression, you know, regulation of expression may play a role in some of the cancers, so we were looking at that, at those issues. And, of course, also the basic molecular composition and structure and structural function type studies, so that kind of studies. But, so '78, I said. I think at that time already we had HTLV-1, so that's another thing that was very exciting at the time. I mean, I'm not personally--I wasn't personally involved in the discovery of HTLV-1. It was done in the virology of, cell biology section at the time. My group was more molecular biology. But once the virus--and it was the first human retrovirus to be discovered. And once that virus was isolated and propagated, then my group got a chance to actually work on the cloning and doing some of the sequencing. So that was very exciting, too. So I think all that was going on at the time of that transition.

Harden: In 1982, you achieved one of those NIH milestones when you became chief of the section of molecular genetics of hematopoietic cells. Now, the first question, was this section created for you and your research, or did you inherit it from someone else?

Wong-Staal: I think it's more an inheritance, because David Gillespie, the man I mentioned about, he was head of--I don't know if it's the exact same title, but certainly there was a section that related to molecular biology that he

was section chief of, and after he left, I suppose I was acting for a while, but it was in ‘82 that I was formally recognized.

Harden: When you became chief, presumably you reviewed where the section was going and what you wanted. Would you describe your goals at that point, what you wanted that section to do?

Wong-Staal: Well, I think it’s very simple, because that was the time when HIV was available, and almost everything we do, we did, was important in the discover. So I think that the plans were straightforward. We need to understand what the virus is at the molecular level. And as it turns out, the virus was very complicated, so we had to identify each gene. There are a number of novel genes not found in other retroviruses. We have to not only to show that they are exist, but what they do. So, again, the structural function of...

Harden: We were just on the verge of it in ‘82. You were then--the virus is not defined yet.

Wong-Staal: Oh, absolutely. Yeah. I get the chronology _____.

Harden: So that’s why, before you hit, we’re going to get to _____.

Wong-Staal: It was in ‘83, in ‘83.

Harden: Eighty-three is when it really starts to get real.

Wong-Staal: Yeah, that’s true.

Harden: Now, in ‘82, we had HTLV-1, so we were doing those things with HTLV-1.

Now, the efforts on trying to find a retrovirus for AIDS were ongoing in the lab. And we were participating in it, but only, you know, doing things like looking at samples from AIDS tissues to see if we can detect sequences related to then known viruses, including HTLV-1. So I think that's the kind of work. But, of course, that's only a part of the program. The other part is really to continue on with HTLV-1 and oncogenes and...

Harden: Well, what I was getting at here was, in the pre-AIDS era, how did you see your career developing and this section developing, and you would have stayed, continued to work on retroviruses. That would have probably been your focus? Or do you think you would have tried to...

Wong-Staal: I think we would--at that time, we were, in fact, doing a lot of interesting things with retroviruses and oncogenes, you know, as many other labs in the country. But we were, I think, competitive in that area: looking at mechanisms of transformation, looking at, you know, again, what the various oncogenes do in the cells, whether they're transcriptional activators, whether they're signal transducers, you know, whatever. So I think that whole program certainly could have continued had not HIV come along.

Harden: Would you just name some of the investigators who were working with you in this section in 1982?

Wong-Staal: Mm-hmm. Ricardo Dalafaber. Actually, he's done really well. He's a full professor at Columbia now. He's the first one to show *mic* gene amplification in leukemia cells, in primate leukemia. Jennifer Fontini, I

mentioned before. She was working with me on, for example, mapping the *fas* gene from the feline sarcoma virus. And, in fact, we published one of the first papers on showing that the cell, the counterpart of this gene, had intervening sequences. There wasn't, you know... But now it's sort of obvious, but at that time, it was a new concept. We were the first to characterize the simian, the *sis* gene, for the simian sarcoma virus transforming gene. In fact, I think we gave the name sis. That was in our first paper looking at that. And the person who was involved or the people who were involved is, I think Ricardo was involved in that too, Phil Lefavre, and also Steven Josephs. He was a technician who then became a graduate student. He got his Ph.D. from American University, and I was his thesis advisor. He's now at, I think, Baxter Pharmaceutical Company. He's a scientist there now. And, let me think, maybe Mandy Mon [?] could have been involved at that time as well.

Hannaway: Do you recall--this is a more general question--the debate over whether human retroviruses existed?

Wong-Staal: Yes. I think, you know, at that time, the dogma at that time, because most of the retroviruses work was done in the murine system and in the avian system, and there was a very high level of virus replication. And at the same time, people who were looking for human retroviruses had some mishaps. I mean, there were a few so-called discoveries that turned out to be contaminations, artifacts, whatever. So it sort of soured people on the concept of, you know, maybe they don't exist. If they existed, then you

would have easy or obvious to get them by now. So I think that there was an--even the really well-respected scientists, and particularly the well-respected scientists, were very strongly against the idea that human retroviruses existed, with few exceptions, and I think Bob is one of the few exceptions, that he very strongly believes that they do exist. And around that time, I think the model of the bovine leukemia virus came about, and one of... I mean, Bernie, who works on the system, happened to be a very good friend of Bob's, and he had a hard time, I mean, Bernie _____, isolating BLV from tumor tissues or whatever. So it was understood that the virus replicates at very low level. So Bob then said, "Look, here's a model that you don't necessarily have very high titer virus, you know, with retroviruses, so there may be exceptions and maybe humans are more like the cow than the mouse. So I think that's sort of kept him going.

Hannaway: What convinced you that human retroviruses existed?

Wong-Staal: You know, I think it's more or less along the same line. I mean, it's sort of not conceivable why humans should be that much different from animals. I mean, there was example after example of retroviruses, be they endogenous or exogenous, found in different animal species.

Hannaway: There was no reason humans would be exempt, so to speak.

Wong-Staal: Right, right.

Hannaway: Would you describe, even though you were not directly involved in it, but give us some general description about the research conducted in the Gallo laboratory related to the discovery of HTLV-1.

Wong-Staal: Yes. I think, really, the discovery or the breakthrough that led to the discovery of HTLV-1 preceded the real discovery, is the discovery of T-cell growth factor, what is now called IL-2. And maybe what preceded that before, even, was the incidence of so-called HL-23 virus. I mean, that was a virus isolated from leukemic patients that. I mean, it's still not clear whether that, there was ever a real virus. Certainly, in the early days, they detected reverse transcriptase activity, and that looks real. But then, subsequently, suddenly the virus that was not growing well became very replicated, highly replicated, and then it turned out that it was artifact contamination. I shouldn't say contamination. And when they tried to go back to re-isolate, they ran out of factors that supported _____. So that really led the program, or one program, or one branch of the lab, to look for factors that support growth of leukemic cells in vitro. And out of that effort came the discovery of IL-2. Once that's possible, then they were able then to grow particularly from T-cell leukemias, and so getting these cells, that first patient, I think he had cutaneous T-cell lymphoma or leukemia. At that time, they thought _____+ or something like that. Yeah. So that using the IL-2 to long-term culture those cells, they were then able to isolate the virus. And, still, it was not a high-level replication, so they--on top of the long-term culture requirement, they also need a sensitive detection method, which was also developed in the lab.

Harden: I just would like to ask one question along these lines, too. Did you happen to be at that fateful meeting at Hershey, where it was disclosed that

the first Gallo retrovirus was a contaminate in other words... Do you remember this?

Wong-Staal: Right.

Harden: The question has never been asked, been answered to my satisfaction is, why did people wait to do this in public? Why didn't they come to him privately?

Wong-Staal: I don't think I was at the meeting, but I certainly heard about it.

Harden: Certainly. You have any thoughts on this, just out of curiosity?

Wong-Staal: Well, who knows. I mean, do you understand human nature?

Harden: Well, I just think it's...

Wong-Staal: I think some people enjoy seeing other people crucified in public. Right?

Harden: Yes, they do. That's what I'm getting at.

Wong-Staal: Yeah, yeah.

Harden: It really is. You think it was a vindictive sort of...

Wong-Staal: Yeah. Bob polarizes people. I think he has people who are very close to him and supportive of him, and he also has people who are very antagonistic.

Harden: So we're not missing some scientific nuance. It probably was a more personal thing to let it happen in public, is all I'm saying.

Wong-Staal: Yeah, I think so.

Harden: I'm not trying to get any things. But it just was not entirely...

Wong-Staal: Yeah. I think it was almost like a set-up. Yeah. To humiliate him.

Harden: All right. Now let's move into AIDS and get some chronology here. We had the first Gottlieb publication in June of '81, and you became the section chief in '82. And, as I recall, Jim Curran came up to make a presentation to the National Cancer Advisory Board, where he saw Bob Gallo and urged him to get into this. And this was mid-'8... Well, this was in August or September of '82. So this is where we're going. But let's back up now. We've got a whole year there. When do you--can you recall when you first heard about this disease? Even before you were involved in the research, what did you hear about it?

Wong-Staal: I think it's probably around the same time. You know, we have M.D.s in the lab. Ed Gelman, for example, you know, you go to meetings, clinical meetings, and they come back and say, "Oh, this is a very interesting disease that's going on around right now," and so on. And so I think that's when we first heard about it. As we began to know more about the disease, I think, based on the experience with HTLV and also based on the experience with feline leukemia virus, particularly, because FELV have sort of the opposite effect. You can cause leukemia, but at the same time they can also cause cytopenia, so two opposites. And what seems clear after the typing of the disease in AIDS, is that it's the T cell that's in trouble. It's getting depleted. So because the tropism of HTLV is so specific for T cells, the same kind of cell that's being depleted, so you sort of have the yin and yang phenomenon. On one side you have abnormal proliferation, and on the other side you have depletion. So it raised the

possibility...Well, first of all, because the transmission pattern and all, so I think particularly Bob was very convinced that it smells just like a retrovirus. And then, secondly is that, because of the tropism of T cells, that made Jim and others to think that it could be a virus related or in the same general family as HTLV.

Harden: And it didn't strike anybody as mystical that the first human retrovirus had just been identified one year and we have this major, what turns out to be a worldwide pandemic of a human retrovirus immediately thereafter.

Wong-Staal: Well, it may be. But, on the other hand, it should also have broken the barrier of credibility. Right? I mean, before, people probably weren't even entertaining the idea that a retrovirus could be involved. But the fact that you do have a human retrovirus that targets particular T cells, it makes this, I think, more plausible.

Harden: Oh, I forgot another question here. In September '81, NCI sponsored a conference on opportunistic infections and Kaposi's sarcoma, and this was the first official meeting relating to AIDS at the NIH. Do you remember this at all? Were you involved in it?

Wong-Staal: That's probably prior to _____.

Harden: Okay. Let's then move right in _____.

Hannaway: Well, now we want to ask, when did you begin to work on AIDS and...

Wong-Staal: I think it's in the period of... Well, I mean, in terms of working on AIDS, I would say in the late '83, early '84 period, when we, as I said, when we were just looking at samples, looking, trying to detect sequences

homologous to HTLV. In fact, we got a couple of samples from France, for example. And--oh, that's in '84. Was that in... I think it's in '84.

Hannaway: Is this Monsieur Shaddon?

Wong-Staal: Shaman?

Hannaway: Shaddon, the man from Haiti, the...

Wong-Staal: Oh, the Shaddon virus.

Hannaway: Yes.

Wong-Staal: Now, that's... Those samples. But I don't know that that's from France. But I was thinking of the Montagnier group. But this is a different source. The Shaddon is from Leibowitch. I think it's from a different French group.

Hannaway: Yes.

Wong-Staal: Right. But at the time, we also got some samples from Montagnier's group that my group looked at and try to see if there's any homology between HTLV, HTLV-1 and that virus. But as it turned out, we couldn't any, you know, it was water. I mean, there was nothing in there that we can detect. But the Shaddon, you know, he's an AIDS patient. I think what we ended up is cloning HTLV from him. He turned out to be doubly infected.

Hannaway: Infected, yes. He was the famous case.

Wong-Staal: Yeah, right. So that was the sort of confusing part of the process.

Hannaway: So this was a very intensive but also confusing period in the research.

Wong-Staal: Right, right, exactly. I mean, we didn't realize at the time that, in fact, many of the AIDS patients were infected with HTLV as well as, of course, HIV.

Hannaway: Would you discuss concerns within your section, or in the Gallo lab generally, about biosafety issues relating to AIDS, working with AIDS viruses and so on.

Wong-Staal: Right, right. It's funny, you know. There wasn't a lot of concern about biosafety. I mean, people would say, you know, "Well, we're careful," as if, I mean, the same precaution one used for hepatitis. I mean, they would work in the hood and so on. But certainly there was no BL-3. There wasn't, you know--things like that didn't even exist. Right? So people were... I mean, in general, you used tissue, aseptic technique tissue culture procedures, you work in a hood, you glove and gown. But other than that, I don't think there were really additional precautions.

Harden: And you didn't have folks in your lab who were really afraid to work on this disease, then.

Wong-Staal: No. Now, my lab was really sort of the molecular lab. I mean, if we say you get AIDS from blood or tissues, we immediately dump STS, pheno extract, so you really get rid of any possibility of infection, infectious material, right away. So we're not really working so much with high-risk material. So you're working with naked DNA. They're not very infectious, so that's not...

Hannaway: We'd like you to describe as best you can the evolution of research on AIDS in the Gallo lab. And I'd like to read a quote from you that was cited by Bob Gallo in his book, *Virus Hunting*. I don't know if you recall making this or when you made it, but you said, "Working with this virus is like putting your hand in a treasure chest. Every time you put your hand in, you pull out a gem."

Wong-Staal: Yeah, I think that's true because it's a new virus. But not only is it a new virus, it's a very interesting and complicated virus. So that means that there's a lot of discovery to be made, you know. The new trans-activated genes, they really... I mean, every gene is a new paradigm for a virus-host interaction. So I think that was a very productive period. I mean, it's sort of dizzying, you know, because there's so much to do. You can't really-- you don't even know what to do first. So, you know, I would say that's really the highlight of my career, is really that period of discovery, intense discovery.

Hannaway: So a period of two to three years there that...

Wong-Staal: Right, mm-hmm.

Harden: Could you outline quickly the... Well, we're going to go through it, but keep in mind that I want to make sure that we cover all of the major contributions that you see that your lab made to the research as we go. One of the first things that you all did was to clone the AIDS virus and published in 1984, _____ the sequence. Now, Mel Martin was doing similar work, and he published a similar paper at [?]. Can you tell me how

the work of the two labs were different, or were they just repeating each other?

Wong-Staal: I think Mel Martin came much later. Didn't he? Because I know that in terms of the cloning, we were the first, the French group was the second, and the San Francisco group was the third. So if Mel did anything, it was further down in terms of cloning. And then, sequencing, again, it's the same three groups that first published the sequence: our group, the French, and Jay Levy's group.

Harden: Was that done before the question of priority arose? Because Dr. Martin apparently was the person who said the two viruses were identical.

Wong-Staal: Oh, that's before. I mean, that's from the sequence that they say that.

Harden: I see, right. But this--what I'm trying to get at is that you all were doing this early on as well. You were doing the...

Wong-Staal: Not as well. We were doing the sequencing first.

Harden: Yes.

Wong-Staal: We published the entire sequence, and the French group published the entire sequence, and the French... I mean the San Francisco group published the entire sequence. And then, in fact, we submitted a paper to--not a paper, a letter, to *Nature* for publication of these three papers. We submitted a letter to *Nature* and said these three isolates obviously belong to the same family, but our isolate and the sequence of the isolate the French isolate seem much more related than the San Francisco isolate.

Harden: San Francisco.

Wong-Staal: And we were thinking that the spectrum of relatedness, which is not wrong. I mean, if you look at HIV, you really have a whole spectrum, some of them more closely together than others. Depends on what end of the spectrum you look at. So the question that Mel maybe took issue with is that, whether the similarity of the French isolate and the isolate that we sequenced really can be justified on the basis of strain-to-strain variation or where there's too much to be expected from that .Now, there was really no point of reference, because if you lo ok at HTLV-1, isolates from, diverse isolates are very similar. I mean, they're as related as two HIV isolates from the same person. Okay? So it's not that we have some standard to go by what should be the degree of variation. So that was totally, you know, no guidelines, in other words. But as we, you know, as more isolates are sequenced, then, of course, then you see more of a pattern of what, how much variation there usually exists among different isolates.

Harden: It became an issue later. That's why.

Wong-Staal: Yes, obviously. But, on the other hand, I should point out, however, that at the same time, I mean, you know, it's almost sort of an unfortunate coincidence that the first isolate that we really did the most extensive studies on turned out to be a potential contaminant, because there were other isolates at the same time from the lab that were sequenced later that was very divergent, you know. One of them is the isolate called RF, and it's used extensively now because it was viewed now as a prototype that's

very different from the 3B isolate and LEI isolate, you know, that were available in the early days. So that virus was around at the same time that the 3B virus was. But it's just because it wasn't being produced at as high a level as 3B that 3B was chosen for the sequencing and analysis. So it's sort of a stroke of fate that...

Hannaway: It's the luck of the draw...

Wong-Staal: Right.

Hannaway: That that was chosen instead of this _____.

Harden: In 1987, you described the R gene of HIV, and I want to show you a couple charts I've been trying to put together here. This was from a 1986 publication confronting AIDS that was put out, and, as you can see, that gene is not known at this point. And then this one was in '88. It was the update for this book. And the R gene is described as "function unknown" at this point. And if I'm understanding it correctly, this is the current list of the way the genes are described, since many different groups were coming up with genes and naming them different things. Your gene--this is the one that you all identified, as I understand it--is now called *vpr*.

Wong-Staal: Right.

Harden: Correct?

Wong-Staal: Correct.

Harden: Now...

Wong-Staal: Vp just means viral protein.

Harden: That's what I thought. All right. Would you explain? It's described here as an accessory gene. What does it do, and what did you... Tell us about discovering the gene and learning about it.

Wong-Staal: Right. You know, at the time we discovered it as an open reading frame. That means that we, you know, from the sequence, it's hard to tell because it's a very short sequence, smaller than most genes that we're used to. But what that paper described is that we can actually show that those sequences express into proteins, and I'm not sure if it's in the same paper, but if not, then subsequently, is that patients who are infected actually make some antibody against that protein. So that's saying that that protein not only... So at the time, we show that open reading frame was expressed as a protein, and, furthermore, that patients infected with HIV actually make some antibody against that protein, so suggesting it's also expressed in the patient. At the time, we called it an accessory gene, function unknown, because it doesn't seem to be critical for virus replication, at least not in T-cell lines that, you know, that's what people usually use in the laboratory, because if you remove that gene by deletion, mutation, the virus seems to do just fine. So it was very puzzling.

Now it turns out to be a very interesting gene. It has unique properties. It helps the... Actually, one of the unique properties of HIV is that it can infect a cell that is resting, not actively dividing. And a typical example of that is the macrophage. Macrophages are totally differentiated. They're no longer actively dividing. And most retroviruses, at least all the

laboratory retroviruses that were known at the time, cannot infect such cells. They need cell division to do it. And what it turns out is that those viruses are stuck from getting into the nucleus. Their viral RNA/DNA complex cannot penetrate the nucleus unless there's cell division, and that's when the nuclear membrane dissolves. Now it's shown that *vpr* plays a very critical role in the process in allowing the virus to get into the nucleus in non-dividing cells, so _____ an intact nuclear membrane. So it's critical. Or if you delete that gene, even though the virus can do well on T cells, its ability to infect macrophages is very much impaired. And then there's another effect of resting cells at a certain stage of the cell cycle. So from a biology point of view, it's also very interesting. But it's a very conserved gene, so it is clear that it does play an important role in the virus biology and pathogenesis and so on.

Harden: Now, you were looking at a lot of, all the different genes at this time, too, and one of them was the envelope gene, coding for the envelope protein. And I believe you were involved in the earliest assessment of antigenic drift in that envelope protein and its implications for vaccine development. Could you talk about that a little bit?

Wong-Staal: Yes. I think, you know, from, again, the early isolations and sequencing from different groups, it was clear that HIV is not a single genetic entity, that there's variation among different isolates. But what was found--and I think we're one of the earliest, if not the earliest, group to show--is that there's also, even from the same patient, if you look at different clones

from the same patient, you can see variation as well. So there's intra-patient variation. And a lot of the variation is in the envelope gene, so that suggests... I mean, that kind of phenomenon has been described for other RNA viruses, and this is referred to as a quasi species. Where you don't have a single species of viral genome, it's a quasi species. And, furthermore, this quasi species can drift. The composition can change with time, with external pressure. And our observation at the genetic molecular level corroborates studies from other scientists in terms of virus re-neutralization also, you know, that very often is type specific that, you know, an antibody from one patient that may neutralize its own virus may not neutralize other virus isolates. But, furthermore, within the same patient, neutralizing an antibody against an earlier isolate may not neutralize a later isolate, so again suggesting the drift. So what we're--our description is really at the molecular level, and then other people have immunological data.

Harden: But it was quite apparent to you early on that it's not going to be easy to make a vaccine because of this.

Wong-Staal: Yeah, correct.

Harden: Okay.

Hannaway: We're interested as well in the large issue of the effect AIDS research had on the NIH and the various institutes. So we wondered if you could comment on what overall changes did you see in the Gallo lab and in your section in response to the emphasis on AIDS research from 1982 until

1989. The sort of things we're interested in are changes in the program of research, in funding, and in personnel.

Wong-Staal: Right. I think the biggest change with AIDS is that suddenly the research that we do becomes or catch the attention of the public, because prior to that, I think no one cared about oncogenes, I mean, even oncogenes, but particularly if it's a yeast gene or, you know, any regulatory mechanisms and so on. So I--and I think that's both good and bad, of course. I think the good part of it is that you feel that even though what we're doing is actually very basic, you know, we're still looking at fundamental gene regulation and structure, gene structure function studies, but suddenly it has a relevance for something important, an important disease. But the negative part is that, you know, you're under the microscope all the time, and people have maybe undue expectation. So the pressure is always on, you know: when's the cure, when's the vaccine, what's next? And that part of it sometimes can be too much. In terms of the funding, I think at the time, I think at NIH, it wasn't too much of a problem. We were getting good support and I think in part justified because of all the progress that was being made. Even outside the NIH intramural program, AIDS research was less supported. But maybe that actually, that led to the perception that if you label your research as AIDS, you can get money. So I think that's also a lot of abuse of the system that people were not really working on AIDS but they label their research as AIDS and get money. And, as a result, I think, in fact, trying to get AIDS money becomes very

competitive because you have so many people coming in. So I think at this point, I don't think it's a particular advantage to be, I mean in terms from the grants level, to be competing for funding, to say that you're working on AIDS.

Hannaway: So that's been a transition.

Wong-Staal: Yeah.

Hannaway: Well, then, our next question relates to what you've just been talking about. We're interested in the effect of all of the publicity and debate over who discovered AIDS on the working of the Gallo lab, and particularly also, did the Freedom of Information requests alter the way in which research was conducted?

Wong-Staal: I think also what changed with AIDS was the issue of patenting. Prior to that, again, you know, we hardly thought of patenting one's work because, you know, the interest in the scientific discovery and the knowledge, but not the commercial implications. So, with HIV, you know, the process of diagnostics and, of course, the cloning and subsequent other things, we were actually told by NIH people that we should _____ patents, and I think--and that's right because it's an important public health problem, and in order to attract the pharmaceutical companies, you really need patent protection of your discovery. But I think because of that, because of the commercial issue, then you also bring in other aspects of profits and rights and shares of equity, royalty, whatever, and that, I think, escalates the problem tremendously.

Harden: That would, and I was going to come back to this, but I'm just going to add this question in. As we go about the Technology Transfer Act of 1986, now, the first patents, of course, for the Elisa test and others came before that, before the '86 act.

Wong-Staal: '86 act.

Harden: So, you all were getting instruction then from the administration that you should pursue a patent on the test and what have you. Was this... And, as you were suggesting, I suppose put some pressure in terms not only of the thought about profit or about other things, but sharing samples, sharing information, whose name went on which paper...

Wong-Staal: Exactly.

Harden: All these sorts of things. Was there a lot of conversation about this within the lab, the investigators themselves? Did you all talk about it and sit down formally and discuss it, or talk about it informally, or was it a real hassle?

Wong-Staal: Not so much at our level. I think, you know, at the time, I think most of the, I mean, the most critical patents is really the blood test, and that--I was not involved. That was really pre-molecular biology, if you will. It's the virus-producing cells and so on. And subsequent to that, I think we just patent everything and we include everybody in our patents, I mean, all the people who worked in the lab. I have to say that the, we didn't have the best patent lawyers at NIH, so a lot of those things, I don't know whether they ever resulted in anything. But...

Harden: But to go back, then, to Caroline's question.

Wong-Staal: Yes, you had a second part of the question.

Harden: Just about the publicity.

Wong-Staal: Oh, the publicity.

Hannaway: And the debate over who discovered AIDS.

Wong-Staal: Right.

Harden: And the inquiries and the whole thing.

Wong-Staal: Right, right, right. You know, as I said, there's no question that Montagnier's group first had the right virus, although what they published was not very convincing and is only from a single patient. Okay? And our laboratory had multiple isolates from different patients. They have, I think, much more--they have a much stronger case for etiology. And, again, repeating what I said earlier, I think it was unfortunate that we had focused on this one isolate that seemed to grow the best, and, as it turns out, the reason it's growing so well is because it's... I mean, that's why it contaminates, because it's growing so well. So... And to really be the first prototype that we analyzed and patented, you know, that produced the cells used for the blood test patent, and so on. So I think, you know, a lot of people are not aware that it didn't happen only one in our lab. It, in fact, happened in Montagnier's lab, the contamination, because when they subsequently, because of all this issue, they went back and sequenced the early samples, that their earliest LAI isolate was not the same as what is subsequently LAI. So they have contaminated their own cells with a more

replicative virus. That happened also in Robin Weiss's lab. I mean, Robin Weiss in England has published the first British isolate, HIV isolate. In fact, we got samples from him. Turned out to be the same virus. So I think it's just, you know, it happens to be a very highly replicating virus and that it's easily contaminating other cultures. So really, the thing to stress is that there were more than one isolate in Gallo's lab, that we could have chosen any one of those to expand our studies on. So it was, you know, again...

Harden: Have you given any philosophical thought to why Gallo took such a beating over this in the United States and was seen as a villain, as opposed to Montagnier being seen as a hero and... I mean, it's more than the fact, is what I'm getting at. And is it Gallo's personality, or is it, I mean, the fact that you said he polarizes people, or is there...

Wong-Staal: I think a lot of it is his personality.

Harden: Or is it the fact that he works for the government?

Wong-Staal: I'm not sure that's that. You know, I think also, Americans have a very different mentality from Europeans. I mean, you know, I know of no scientist, whether European or American, that really respects Montagnier for being a scientist. I mean, he's not a good scientist. I mean, I can say that on tape. But, and yet, the Europeans rally against, you know, around him. They protect him, they want to push him as the discoverer. But Americans want to destroy their own heroes, so... And I think that's the major difference. That could be, you know, competitiveness, it could be

jealousy, and it also could be a lot of people who don't like the style that Bob goes around doing science. I mean, he's very aggressive, he does, you know... I mean, sometimes he does, if other groups make a discovery and he would say, "Well, why can't we," you know, "Why couldn't we have done that first or thought of that first?" And so _____ even thought, you know, "Bob, let other people do something. We don't have to make all the discoveries and do everything first." So, I mean... But he does have this attitude that, to win, you know, to achieve, and I think that turns off a lot of people. So I'm sure a lot of it is personality.

Hannaway: But he's not the only competitive scientist out there.

Wong-Staal: No, no. I think there are. But I, you know...

Harden: Well, I think that...

Wong-Staal: He's not the only scientist that's being persecuted either, so...

Hannaway: Right. Well, some people have...

Wong-Staal: The bigger you are, the harder you fall.

Hannaway: Some have said that what's not understood, which I think you were talking about just a moment ago, is the way that people, especially virologists, interacted, you know, the different labs, interacted. They would routinely send each other samples and tell each other of their findings in informal ways.

Wong-Staal: Prior to all the _____.

Hannaway: Prior to all the... And this aspect of the sort of what historians or _____ call the culture of virology is not understood in general.

Wong-Staal: Right, right.

Harden: And there is also the assumption that I think is out there that scientists working on medical research should have, know the goal, to be Marcus Welby and hold people's hands, and the intellectual give and take and the personal goals for achievement are not considered in this. When someone is--what's the word I'm looking for--strong enough to let that show that he wants to achieve...

Wong-Staal: Well, they're human.

Harden: They're human, yes. Then it can sometimes come down on them. Let's broaden it a little bit here and see if you will talk a little bit about what kind of interaction you saw on the NIH campus among the various institutes working on AIDS, especially NCI and NIAID. Were there NIAID people collaborating with you, for example?

Wong-Staal: Let me think.

Harden: Again, I'm still in the '80s.

Wong-Staal: Right. Well, we were collaborating with Warner Greene, but I think he's in the NCI, I don't think he's NIAID. But also, mostly on HTLV rather than HIV, although I think we did exchange... I mean, we certainly gave reagents to NIAID people, clones. That's how the whole...

Harden: Were you going to the same seminars?

Wong-Staal: Oh, definitely, yeah, yeah. I mean, in the beginning, yeah.

Harden: Yeah.

Wong-Staal: I'm sure they, we have... Gallo has this annual _____ meeting that was open to other people at NIH. I think a lot of Tony Fauci's people come, for example.

Harden: What about interactions in the Clinical Center? I know we interviewed Sam Broder. He was talking about being able to see a patient today and get the latest results from your lab, and then try to put things together.

Wong-Staal: Oh, yeah. I forgot about Sam. Yeah. I think Sam Broder was very close to the lab, and he was very involved in, you know, trying to treat HIV infection. So there was a close interaction there.

Hannaway: You didn't see any competition between institutes or for getting recognition for their AIDS research or...

Wong-Staal: There may be some, but I think in the early days, our lab just so dominated the field that really, you know, I think there wasn't any attempt to take that away from us. So there's more collaboration, I would say, you know. Like, for example, Broder's expertise or interest is complementary to ours rather than competitive. And the same thing with Tony Fauci's. I mean, he's more immunological aspect, and certainly we're not immunologists, so it's more productive interaction.

Harden: So it was a breaking down of the problem. In other words, you had expertise in this area, and he was an immunologist. We were looking at the elephant in many different ways.

Wong-Staal: Yeah, exactly.

Harden: But you think this was probably the most productive way to go.

Wong-Staal: Right, yes, because you... I mean, studying HIV is, you really need a multidisciplinary approach, so it's good to have all the expertise together.

Hannaway: The NIH, as you well know, has been criticized by activists and in the media for the slowness of its response to AIDS.

Wong-Staal: Mm-hmm.

Hannaway: How would you personally characterize the NIH's response to the AIDS epidemic, with special reference to the intramural program?

Wong-Staal: I don't think we're particularly slow in response. I mean, certainly not at the laboratory level. I mean, we did the best we can, and I believe we were getting the support from the institutions. It may be at the second level, the translation of the discovery to implementation of whatever, you know, diagnostics or other types of...

Hannaway: You think that was not as effective or...

Wong-Staal: No. I'm not saying that I don't think that's as effective. But what I'm saying is that their comments could have been directed at that aspect of the process.

Harden: Well, they were dying, and it was a new disease, and nobody knew what to do.

Wong-Staal: Right, yeah. Because, I mean, what we do in the laboratory is not immediately, you know, available to them anyway, so... And also, if they're infected, they're not interested in the diagnosis. They're really interested in the treatment. And of course, you know, we still don't have very good treatment, so it's a big problem. Actually, now that I think of it,

I didn't respond to one part of your earlier question, which is the, you know, all the Freedom of Information and all that. I actually am very lucky because I left right at that time, when the timing was starting, because I left in the beginning of 1990. I think that process started, you know, in 1989, '90, around the same time. So I wasn't really subjected to a lot of that. But I do have, you know, of course, interaction and contacts and discussions with people who stayed behind, and I know it was very demoralizing, and it sort of almost paralyzed the lab. I mean, it's really to the lab's great credit that it continues to make discovery and progress because, you know, as you can imagine, it's not only the mechanics of the process, you know, they're to provide documents upon documents, and it's all-consuming. But it's also from the the spirit of the lab. I mean, no one wants to be criticized and, you know, be looked under the microscope and so on. So I think it's really a very dark period, at least in the history of that lab.

Hannaway: Yes.

Wong-Staal: Maybe not all of NIH.

Hannaway: When you were at the NIH, were you involved in any of the inter-institute committees or task forces relating to AIDS?

Wong-Staal: Well, I was on the task force that Gallo formed, but it's not really inter-institutional but it's international, because he was including a lot of people, actually, a lot of scientists from Europe, including Chermann and Montagnair.

Hannaway: Yes.

Wong-Staal: But also Leibowitch and also _____. I mean, people from all over the country participating, and other countries too.

Hannaway: So this was really a Cancer Institute-organized task force?

Wong-Staal: Well, it's actually an NTC-organized task force. It's a self, you know.

Hannaway: Yes.

Wong-Staal: I don't think it has the mandate of the Cancer Institute.

Hannaway: No.

Wong-Staal: But Sam Broder certainly was a part of that, and he's the director of it.

Hannaway: Yes.

Harden: We've asked everyone, and gotten a lot of different answers. Were you or your family, did you ever encounter any negative reactions when people found out you were working on AIDS? Did they stop shaking your hand or get up and leave your dinner table or anything like this?

Wong-Staal: No, actually, on the contrary. I mean, when they find out I work on AIDS, usually they're very interested. It's a good dinner conversation. They're curious, you know, what's going on and so on. I think, actually, I think people are pretty--I mean, surprisingly, that know that the virus is not that easily transmitted. I think that part of it, how you catch the virus...

Harden: Even early on.

Wong-Staal: Oh, I see, the very early days. I think maybe a couple of instances when people, you know, they don't... But it wasn't a general phenomenon.

Harden: Your brothers and sisters didn't say, "Are you crazy"?

Wong-Staal: Oh, no. I mean, my mother was saying, you know, "Are you sure it's safe?" and I explained to her that, you know, you do protect yourself with gloves and so on. So it wasn't a big issue.

Harden: Now, you have moved, through your career, from hands-on work in the laboratory to being a section chief and then, of course, now you're a chaired professor. How do you feel about the different roles of people in the laboratory, and do you miss having your hands in the laboratory more when you're directing as an administrator, if I'm making my question clear?

Wong-Staal: Mm-hmm, yes. I think part of it. I think it is fun to work in the lab. But it's also very frustrating because, you know, things only work part of the time, you know. I mean, I think the euphoria is probably outweighed by the frustration. So, in that sense, I think being a group leader and having a group working with you is a little better because, first of all, you can step back and look at the whole picture instead of being obsessed with the minute details. And you determine the general direction of where things can go. And, you know, I mean, I'm not experiencing the daily frustrations, for one thing, but people actually come to me when they have something interesting, and then we discuss, oh, you know, what should we do next, and it's... So, and even that part of it is a more positive experience, although, you know, it is not _____. I mean, I don't feel like I make the discovery with my own hands. So that part of it is... So it's a

tradeoff, I would say. It's a tradeoff. But I feel now, at this stage of my career, I'm better at doing the overall direction than working at the bench.

Harden: At the bench.

Wong-Staal: I can probably even accomplish, I mean, I know I can accomplish more this way than being hands-on.

Harden: The Gallo lab was very large, and some people were criticizing, when they were looking at some of the problems that arose in the various international questions, that maybe it was too big a lab and that it was not easy to keep tabs on 60 people. And then there was the situation when the Cancer Institute cut back on administrative support people. And do you recall any of this as being major problems in the research on AIDS while you were there?

Wong-Staal: I think there are pros and cons of a large program. I think, on one hand, NIH is the only place really where you can have a program at a group; I mean a larger, a reasonably large group, but with a central mission to do something, and then you have this, again, you know, different multidisciplinary approach that complement each other to achieve a defined goal. You can't do that in a university, because in the university, each lab is, you know, its own, has its own set of goals and, you know, you have individual investigators that really sometimes collaborate, but they're not forming part of a whole program. So that part of it, you know, I think it's a tremendous opportunity to have intramural programs like that. But, of course, I mean, there are instances when you can't, you just can manage

a group directly of that size. So then it really depends on the leadership and capability of the lab chief, whether he's able to delegate to competent people to oversee a subset of those groups, and how they can still centralize all the resources and coordinate and so on. So you can say that maybe it's anti-intellectual because you're really working as a group rather than, you know, individual, sort of our own type investigator-initiated type research. But, you know, perhaps that's what NIH should be about, that you have group efforts. So people always talk about Manhattan Projects. I think that is like a Manhattan Project when you have different groups working towards a common purpose.

Harden: Before we move into more recent work, I want to stop and think back over what you have told us about your contributions to AIDS while you were here in the intramural program, and tell us now what we've left out, perhaps, if anything, that you think ought to be noted.

Wong-Staal: No. I mean, we were the first to obtain molecular clone, well, the first clone and then multiple clones to actually show that molecular clone have biological activity; that is, it has the same--it depletes T cells in culture also. So I think that really proves the virus is the agent, because, you know, sometimes you can isolate a virus from a patient, but it could be opportunistic, and that doesn't mean that there's a causal relation. But if what you see the virus can do in tissue culture and using molecular clone, that is, there's no other, you know, genetic information associated with it that can do the job, then I think it provides a stronger proof that the virus is

the causative agent. So I think the so-called _____ hypothesis should be put to rest. We also, I think, were the first to describe the genetic diversity from different patients, both inter-patient and intra-patient. Our group, my group, first described the detection of HIV in the brain. What else? And then all these genes. I mean, we actually were the first one to identify the *tat* gene, which is a critical regulatory gene for HIV--it's transcription activated--and then defined some of the mechanism and function of other regulatory genes.

Harden: Okay. Why don't we move on, then.

Hannaway: In 1990, you were appointed to the Florence Rifford chair in AIDS research at the University of California-San Diego.

Wong-Staal: Mm-hmm.

Hannaway: Left the Cancer Institute.

Wong-Staal: Mm-hmm.

Hannaway: Would you tell us how this came about? And also, what differences do you find between doing research in Bethesda at the NIH and working in an academic university setting?

Wong-Staal: I think I was at a stage of my career that I feel that, much as I admire Bob as a leader and as a scientist, his visibility is really overshadowing me. Although I think we really have complementary expertise, and people recognize that I'm doing molecular biology and he's not. But still, I think the association is sometimes, you know, works against me. So I thought it's time for me to move. And I think, also, part of it was also because of

the, in fact, the Quidson (?) article that came out and the beginning of the process for Freedom of Information. So I thought, you know, I need to get out of here. So--and I chose San Diego because I did a year postdoc there after UCLA, and I loved the place, and I think it's a very good scientific environment because it's not only the university there, there's also Scripps and Salk and, you know, the La Jolla Institute for Allergy and Immunology. So it's a very rich scientific environment. So, in terms of the differences in operation, well, first of all, you know, really for the first time, I'm completely my own boss, so that's very exciting.

Hannaway: Mm-hmm.

Wong-Staal: The ability to have students and young people is also very exciting. Everything at NIH, you know, at least when I was here, it was very difficult to have students. I've had a couple of students, you know, my technician who went to...

Hannaway: American University.

Wong-Staal: Yeah, American University, and so on. But, you know, it's very rare instances. And at the time, most of the postdocs at NIH were only through the Fogarty Center, so you really only get the foreign postdocs, and then the rest, you know, are much older people. So I think the difference between university and the NIH is really the youth and the energy that you get from students and from younger people. Of course, it's also a very different environment in that, you know, now I have to worry about also my financial situation, you know, grants and so on. So that part of it is

somewhat of a struggle, I mean, especially in the beginning, because I have to learn the process, you know, from being, from a protective environment to that. But it's not getting very much easier, I have to say. And then, you know, having to teach, which I was worried about in the beginning...

Hannaway: You were discussing granting and teaching.

Wong-Staal: Yeah, oh grants and teaching. Teaching, in the beginning, I was not looking forward to, but now I'm beginning to enjoy it. I think it's good to have the interaction with students and so on.

Hannaway: Would you tell us about the Center for AIDS Research that was set up in 1994 and of which you're the director.

Wong-Staal: Right, yes. Well, I mean, actually, the Center program is from NIH, as you well know. It's sponsored by NIAID, at least at the time. Now I think they're bringing in other institutes as well. So they wanted to establish different centers of excellence, I guess, in AIDS research in different parts of the country, the ideas that, you know, if there's already active research there, maybe they can provide the glue that pulls things together by providing for resources and administrative structure and so on. So we put in an application for competing, and we received, I think, one of 11 Center awards. Separate from that, the university was also, wanted to start an AIDS research, sort of something the equivalent of a department, but it's not called department, it's called an organized research unit. And we refer to that as the AIDS Research Institute just to be different from the Center,

because the Center is a temporary... I mean, hopefully it's not a temporary thing, but it may be a temporary thing. So what we're hoping is the AIDS Research Institute would be permanent. So it went to the dean, and then it went through the agent--not the agent, the regents, and it's really a universally wide. It's not just UCSD, but UC and the whole UC system.

Hannaway: Yes.

Wong-Staal: It was approved. So I was named director of both.

Hannaway: Yes.

Wong-Staal: So it's, we're, you know, it's a big challenge. But I think because with all the both basic and clinical research and work at the university, and in the region, in San Diego, it's very necessary to have this structure there.

Hannaway: Have you become more involved with the clinical side of AIDS research since you've been in this new position?

Wong-Staal: In a way, yes. I'm actually, since I moved to UCSD, I've become interested in gene therapy. It's really a marriage of molecular biology and medicine.

Hannaway: Yes.

Wong-Staal: So--and I've been pushing for that, and we actually have one of the earliest gene therapy trials for HIV patients in the country, so...

Harden: I want to come back and go in a bit more detail...

Wong-Staal: Okay.

Harden: Through all of that. And I want to start by dropping back and showing you two schematic diagrams. This one, Howard Temin did in 1986 of the HIV

life cycle, and as near as I can tell, this was the diagram that informed the first efforts to develop antiviral drugs. I mean, you basically have the three points that you, where it is obvious to intervene with the reverse transcriptase or the integrase or the protease inhibitors, or at the point of infection and what have you.

Wong-Staal: Right.

Harden: Now, this second diagram is from one of your papers.

Wong-Staal: Mm-hmm, yeah. I recognize it.

Harden: But it has some similarities, but it's a lot more sophisticated. And what I...

Wong-Staal: Much more sophisticated.

Harden: And what I want you to do is tell me what we've learned from here to here, and how people were thinking in 1986 and people are thinking now about ways to intervene...

Wong-Staal: Right.

Harden: In it.

Wong-Staal: I think Dr. Timen's scheme is really outlining the different steps for the virus replication, and then imply that each of these steps can be interfered with.

In my scheme, I'm actually putting down what are the strategies that intervene with some of these processes.

Harden: But you walk them through it.

Wong-Staal: Right. So, for example, I put here ribozymes and antisense can act at the time when the virus comes in because the genomic information is RNA.

So ribozymes essentially recognize the specific RNA by sequence complementarity and then inactivates it by cleaving it up. So, and antisense at the same time hybridizes the RNA genome and then prevent it from being utilized essentially. _____ CD4 acts as a competitor at the level of binding of the virus. So those would be strategies to stop the infection event so you prevent the establishment of infection. And I draw this line there because that separates the early events from the late events. You can also have strategies that do not prevent infection per se, but would prevent expression of the virus. So even though the cell is infected, it's not making more progeny, you know, viruses. And, again, the ribozyme can work at this level as well because it can work on the level of the messenger RNA as well as the genomic RNA that needs to be repackaged into these progenies. Tar decoys, now I've mentioned we discovered the gene *tat*, which is a critical gene for regulating virus expression. And tar is the RNA that binds to *tat*. So for *tat* to work, it has to bind to that RNA on the virus genome. Now tar decoys is that you express that RNA element as a decoy molecule, so it competes for the binding of the tat protein, so it prevents, you know, pulling it away from its normal function. And people have used that, in fact, including Gallo's lab, these tar decoys for virus inhibition. Trans-dominant rev protein. Rev, again, we also did one of the earliest work demonstrating how rev works in the cell. And Gary Nable is using, has a gene-therapy approach using trans-dominant rev, which means that it's a mutant form of rev, which is

not only inactive, but it, again, interferes with normal rev function. So, again, because rev is critical for HIV replication, you can also inhibit virus that way. RE decoy is like the tar decoy except now, instead of binding to tar, it binds to rev. So, again, it prevents rev from working. So these--the *rev* gene does not prevent transcription, but it prevents, it interferes with the processing and therefore utilization of a subset of the viral messenger RNA. So it's post-transcription of regulation in its interference at that point. Actually, that didn't turn out--some studies from George Pavlakis's lab that have not been reproduced. I won't even talk about that. And then you can also use other strategies like the trans-dominant gag protein as a mutant gag protein that prevents the assembly of the virus. And you can also have transdominant envelopes, and finally what I would call envelope traps, is that, you know, if you, envelope binds to CD4, for example, that if you express intracellular CD4, you can trap the envelope inside the cell. The alternative is you can also express antibodies to envelope, intracellular single-chain antibody. So, again, it binds the virus envelope inside so that it doesn't, is not free to become incorporated to form the new virus. Now, our approach is using ribozymes. But I was--this is a review, I think...

Harden: This is a review, yes.

Wong-Staal: So I was listing different approaches.

Harden: All the different ones. Now, with all these different ways to attack the virus, how come we haven't inactivated it yet?

Wong-Staal: Well, I think gene therapy has enormous potential, but there's also a lot of technical hurdles because having the gene that will stop the virus is only the first step. The next part is, how do you get the gene in the right cell in sufficient amounts? I think that's the, you know, hurdle that we're all trying to get over.

Harden: And the thing... I believe there was something in this week's *Science* magazine, or one of the recent ones, about the naked DNA, plasma DNA, seems to look very promising.

Wong-Staal: Yes, yes. But that's really using gene... I mean, it's gene therapy for vaccination, I mean, to stimulate the immune response. So it's the gene vaccine approach...

Harden: Okay. Rather than a therapy approach.

Wong-Staal: Right. Because what we're doing here is trying to inhibit the virus rather than to stimulate the immunity, because for stimulating the immunity, you just need to get the gene in, some gene in, to have some level of virus, of expression of that protein. But to inhibit the virus, we have to get it in at least a significant number of the functional target cells.

Harden: And how do you think--which approach is going to work? The ribozymes is what you're putting in your...

Wong-Staal: Yeah. I mean, these approaches are all sort of equivalent, except that we prefer the ribozymes for many, I mean, for a number of reasons, because it's RNA, it's not immunogenic, but also, it's not a single gene, because a ribozyme, you can design it to match any part of the virus genome. So

essentially, we can have a dozen different ribozymes that recognize different parts of HIV and attack it. And, you know; now we're all aware that you can probably never stop the virus with one drug because of resistance. I'm also convinced that you can never stop the virus with one gene because, for the same reason. So with ribozymes, you don't have one gene, you have many genes that you can link together because they're really small molecules. So that's why we go after that approach.

Harden: Where do we stand at this point? Are you still working at it at the laboratory level in vitro? Or is it ready to move into trials, clinical trials?

Wong-Staal: We have, we are doing...

Harden: You said you've had one clinical trial.

Wong-Staal: Yeah. We are doing a... We're gotten into three patients. But the design of the trial is not to treat patients per se. It's really to see whether the gene we're putting in persists, first of all, and is expressed, and whether, you know, in the design of the experiment, we actually take the cells out of the patient, put in a vector that expressed the ribozyme gene, but we also put in a different population of cells, a vector that expressed the control, I mean, the vector alone, without a ribozyme. So the idea is really compare the two populations in the patient to see, because if the ribozyme is doing its job, it would not be infected by HIV, and therefore it should be around, persist longer than the control, because that can be infected and then it can be killed. Just to see if it's functional in that sense. And we, actually, we were not working under optimal conditions because our vector level, titer,

is too low. But even so, in one patient we can tell that the ribozyme is functioning, that it is being selectively expanded over the control vector _____ cells. So that's the first part. But the second part is really to increase the efficiency of gene transfer, and I think there are, you know, that progress is being made that can lead to that. The next problem, I mean, issue, is really the way of introducing the gene. Right now, because of, again, because of the vector's efficiency, we have to take the cells out to put in the vector and then put the cells back. This is called ex vivo manipulation, which is very impractical, you know, especially for developing countries.

Harden: Yeah.

Wong-Staal: You can never...

Hannaway: Try to do this on a large scale.

Wong-Staal: You can never do it on a large scale in, you know, countries that don't have the expertise particularly, and that's, of course, where the impact of the epidemic is.

So we're also working on getting, perhaps, vectors that can be directly injected into the patient that will deliver the gene. And, ironically, I think my personal and I think a lot of other people are thinking along the same direction, is that perhaps the best vector to do that is HIV itself, if you can turn HIV now into a vector for delivering the gene that would kill itself.

Harden: That's ironic, isn't it.

Wong-Staal: Yes. I mean, it's sort of poetic justice.

Hannaway: Killer virus kills virus. Yes.

Wong-Staal: Right, right.

Harden: I'm smiling, though, as you're talking, because what I keep thinking is that you were talking about the really exciting days in '84, '85, '86, but I don't think today is any less exciting, to watch you talk.

Wong-Staal: That's true, that's true. But it's just the pace of discovery is less. I mean, before, this actually was easy because everything you do was discovery. Right now it's more challenging, but it's no less exciting. You're right. I think it's...

Harden: And that's it.

Wong-Staal: Mm-hmm.

Harden: Okay. Well, why don't we go on to 31.

Hannaway: Yes, I think so. You've mentioned the annual Gallo laboratory meeting on AIDS. You continue to participate in that.

Wong-Staal: Mm-hmm.

Hannaway: Do you have any major collaboration going on with members of the Gallo Institute in Baltimore?

Wong-Staal: Not actively, although we have talked about collaborating somewhat.

Hannaway: Because they also are interested in developing therapies, we understand.

Wong-Staal: Yes, yes. And so far, they have not had a major program on gene therapy, so they're more interested in cytokines, chemokines, the small-molecule approach.

Hannaway: Mm-hmm, yes.

Wong-Staal: Which is okay, you know. I don't need the competition. There's enough competition.

Hannaway: Now you have the right to want more competition.

Wong-Staal: Right.

Hannaway: Do you have any collaboration with David Ho's group in New York?

Wong-Staal: We've had off and on in the past, not really that much _____. Again, I think we have sort of--we have taken different direction, I guess.

Hannaway: Yes.

Harden: We've more or less talked about what I had in order as the next questions, about the gene-therapy approaches that you're working on.

Wong-Staal: Right.

Harden: So maybe I'll just ask you one question we have asked to everybody. If AIDS had appeared in 1955 instead of 1981, how would the scientific community have been able to approach it?

Wong-Staal: I think it would have been a disaster because, I mean, again, even after HTLV-1, there was a lot of resistance in thinking this was a retrovirally transmitted disease. I mean, there were still theories of antigen overload, you know, whatever, at that late stage. So I think mentally, they would not make the connection, at least not as readily. The technology for growing T cells was not there, so that...

Harden: T cells were not there.

Wong-Staal: Right, exactly. You're right. So the ability to isolate the virus was not available. Reverse transcriptase was not there.

Harden: That's right.

Wong-Staal: So I think it would be unimaginable. It probably would have killed off most of the human race, at least in Africa, I would say.

Harden: Okay.

Hannaway: I mean, epidemiologists might have some understanding of how it was transmitted.

Wong-Staal: Right. That's true.

Harden: Figured it out, that it was sexually transmitted, blood-borne.

Wong-Staal: Right, right. That's true. So from a prevention point of view. But by then, so many people would have been infected that...

Hannaway: One policy question. When you were at the NIH, you were associated with Sam Broder's work on AZT, and you were familiar with NCI's ongoing empirical work screening compounds for potential anti-cancer activity. I'd like to ask, do we know enough molecular biology to really hope for a rationally designed AIDS therapy in the near future? Or is it going to be the long-term future?

Wong-Staal: I think there has been a lot of effort in rational drug design based on our knowledge of the virus. For example, you know, linking, I mean, some of the decoys, what they call aptimers, for interfering with *tat* and *rev* and so on. The problem with HIV is really, when I first _____, using a drug approach, because now, you know, it's also Tony Fauci's recent studies. A person who's infected probably needs to be treated forever. The virus, once it's established itself in the reservoir; you can never get rid of it. And

anytime you withdraw drugs, the virus comes back. So you have to, you know, treat the patient for three decades maybe, you know, two or three decades. And to maintain a drug at that high a level for such a long time, first of all, you can have cumulative toxicity, the problem of resistance is... You know, so that's why you also not just need one drug, you need three or four drugs, and also mix the regimen. Very difficult, I think. You know, there are compliance issues. It's overwhelming now because it's hard to juggle all the different drugs that are supposed to do different things at different times. I think logistically, it would be just very difficult with a small drug approach. I mean, that's why I personally came to gene therapy. I mean, you need something that's just working all the time for you without worrying about it.

Harden: Can you project a time frame for gene therapy to be effective?

Wong-Staal: Well, unfortunately, I think that is the hard part. It's hard to say. It certainly would not be in the next five to 10 years. It may be beyond that. So, in that sense, I think it's good to have the drugs, at least to keep patients going for a while.

Harden: At this point.

Wong-Staal: Right.

Harden: How would you advise policymakers to think about this, about approaching... They have to deal with constituents who are ill and constituents who don't want to spend too much money on this or that. How should they balance out the spending on basic molecular biology to

come up with some sort of rational design, versus empirical, let's try this, let's try that.

Wong-Staal: Right. Well, I think, first of all, I think AIDS research... You know, a lot of people say, "Why should we support AIDS research when we can support basic research?" But, in fact, AIDS research has been very beneficial to basic research. I mean, from this model, this system, you know, we gain a lot of insights on basic molecular biology and virology and immunology. So it's not all just practical. Now, but in terms of the sort of more practical, applied part of the research. And then you have to think of it this way, is that this is a window of opportunity. I mean, this is one of few diseases or major diseases that we have a defined course. I mean, the cancers, a lot of the cancers, we still don't know what causes them. Right? But here you know the virus cause them, and if you can stop virus, you can stop the disease. So, I mean, it's a defined target even though it's a very slippery target. I mean, it's there. So we shouldn't lose sight of that. And the second part of that is that AIDS, you know, as you know, is--the victims of AIDS are usually young, productive people, and that we are in fact losing a lot economically, I mean, losing a lot from this disease, while some of the other diseases may be targeting more the older population. So there is, should be a motivation to keep this under control. So hopefully, I think it's that this is a temporary measure. You know, you don't need to make the investment forever. Hopefully, something will come out of it. But up to a point, I mean, some people may be right, is that

putting more money in it may not make the process faster because there's only so much one can try at the same time to see what works and what... So a more coordinated, rational approach is more important, rather than the trial-and-error type of approach.

Hannaway: The sort of coordinated activity that you're involved in currently.

Wong-Staal: Right. Yeah, yeah. And then the other part, of course, I think, you know, the vaccine program is very important because prevention ultimately would be, you know, the most effective means, if not for education, which I'm still understanding why it's not working. It has worked to some extent, I guess, but it's not the final answer. But a vaccine would be very important.

But we also shouldn't be under the impression that that's all we have to worry about, that therapy is solved. Therapy is not solved because of this problem.

Harden: One question I forgot to ask earlier. You're now on the NIAID Board of Scientific Counselors. How is the Board as a body advising NIAID to proceed on AIDS research intramurally?

Wong-Staal: Yeah, intramurally. Actually, we have just been evaluating each lab within NIAID rather than a global policy approach. But I think we certainly endorse the vaccine effort, including the vaccine research center that's supposed to be formed here. I think there's a lot of good work going on within NIAID and it certainly should continue to be supported at a high

level. It may be useful if there's more coordination in some parts of it, I think. I think overall it has a good, there's good coordination.

Harden: Well, we're winding down here, but I'd like to know if there's anything else, from start to finish, that you think of that we haven't touched on that you'd like to bring up.

Wong-Staal: I think you've been very exhaustive.

Harden: We try, but...

Hannaway: And exhausting?

Wong-Staal: I didn't say that.

Harden: Well, we want to thank you very much for speaking with us.

Wong-Staal: Thank you.

End of Interview