

This is an oral history interview with Flossie Wong-Staal, Ph.D. about the National Institutes of Health's response to AIDS. The interview was conducted at the National Institutes of Health (NIH) on 10 December 1997. The interviewers are Victoria Harden, Ph.D., Director, Office of NIH History, and Caroline Hannaway, Ph.D., 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: I grew up in a family of four children, two boys and two girls. My father Sueh-Fung Wong, was in the import-export business. My mother Wei-Chung Chor, 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 had the concept that girls should not have higher education, and, on the contrary, they were very happy and pleased and proud of my accomplishments. 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 see me have the opportunity.

Harden: Where did you come in the birth order?

Wong-Staal: I was the third.

Harden: Were you interested in science as a child?

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

Hannaway: 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 Maryknoll was actually run by American nuns, but the system in Hong Kong is the British system.

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's McGill University. I had friends or classmates who were coming to America, and specifically going to UCLA [University of California, Los Angeles], where I ended up. It was part of the desire to be 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--through the television, movies, whatever--the West Coast in America.

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 liked the subject.

Hannaway: There was not a teacher or a specific person who inspired you?

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, it was an era when there were a lot of exciting things happening. Cloning was discovered with the restriction enzymes, so things were just becoming possible. I think also the oncogenic viruses and the reverse transcriptases also were discovered 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.

At that time I remember that there was an article by Gunther Stent [Gunther S. Stent, Ph.D.] published somewhere, "The Rise and Fall of Molecular Biology." He thought that it was the peak of molecular biology, and from then on, it could only go downhill. But, of course, that was very premature. I think it was the right choice. At the time, 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 was an older botanist, but then he turned into a molecular biologist. He was very nurturing, sort of like the grandfather type. Overall, it was a very good experience because of his caring attitude towards his graduate students. At UCLA, molecular biology was not a department. It was an intradepartmental institute. We got to interact with people in chemistry and in microbiology and so on. It was a very positive experience.

Harden: What was the name of your thesis advisor?

Wong-Staal: Samuel Wildman, Ph.D. Again, you know, as I said, he's an older person who worked mostly on tobacco mosaic virus (TMV) but also on 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 were happening.

Wong-Staal: Right.

Harden: In thinking back in terms of what we know now and what was known then, are there particular things that stick in your mind as being just the most exciting?

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 are so many new technologies that have been developed. I always thought that if I could use the techniques we have now to go back to our thesis, I could have done so much more.

Harden: When you arrived at the NIH in 1973, you were a Fogarty fellow. What led you to come to the NIH at that point?

Wong-Staal: Well, at that point, it was partly personal, because my husband, Stephen, [Stephen Staal, M.D.] was assigned to NIH. I had just been married for a couple of years then, so that was the clear necessity. But also, there are several labs at NIH that had interests that match mine. One of them, of course, was Gallo's lab [Robert Gallo, M.D.], because he was trying to identify a pathogenic human retrovirus. At that time, the studies on animal retroviruses were in full swing, and there was a lot of excitement about oncogenes and so on, of retroviruses. I thought that was a very attractive area to get into.

Harden: So your husband and you both had scientific appointments when you came to NIH.

Wong-Staal: Right. He had an appointment first, and then I applied to a few labs.

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. 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 a citizen, just for the record?

Wong-Staal: I think it was 1976.

Harden: 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 was intracisternal A particles, how they replicate, the biochemical analysis of intracisternal A particles. David Gillespie [David Gillespie, Ph.D.] was a section chief within the lab, and he's the person who actually innovated the hybridization procedure with Sol Spiegelman [Sol Spiegelman, Ph.D.]. I also trained with him to learn some of these molecular techniques, hybridization.

Hannaway: You decided to stay at the NIH, and you held positions as a 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 don't have to write grant proposals, and you don't have teaching obligations, and there are a lot of opportunities for interaction. It's also the center of

biomedical research, sort of the mecca. People come and give seminars. It's a very exciting place. It's hard to find a comparable environment outside, especially in a period when you want to have maximum productivity, because any move means downtime at critical points in one's career. I think once you're at NIH, there is a great inertia to leave NIH because you're used to all these privileges. But at the same time, at some point, it's good to have a change.

Hannaway: We will come back to your later career. Would you 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: 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. Sometimes it's hard to dissociate these two minority standings. I see it happening sometimes, and sometimes it's really subtle. At the higher level of decision-making, that's when the old boys' club operates. But when I was young and starting out, I did not see much discrimination.

Hannaway: In 1978, you became a senior investigator in the Laboratory of Tumor Cell Biology at the National Cancer Institute [NCI]. Can you tell us a bit about

the research you were focusing on in the period before the advent of AIDS?

Wong-Staal: We were looking at the primate retroviruses, particularly the gibbon ape leukemia virus and some of the animal transforming viruses, simian sarcoma virus, AMV [avian myeloblastosis virus], and so on, as models for eventual application to the human system. The monkey virus, of course, is relevant because it is an exogenous virus that causes disease and is horizontally transmitted. We were studying oncogenes, because they're homologues of cellular genes. We were interested in whether their expression may play a role in some of the cancers. We were also doing basic molecular composition and structure and function type studies. I think by 1978 we already had HTLV-1 [HTLV-1 was originally known as "human T-cell leukemia virus type 1" and later as "human T-cell lymphotropic virus type 1"]. It was another thing that was very exciting at the time. I wasn't personally involved in the discovery of HTLV-1. It was done in the cell biology section at the time. My group was more focused on molecular biology. HTLV-1 was the first human retrovirus to be discovered. Once that virus was isolated and propagated, then my group got a chance to work on cloning it and doing some of the sequencing. That was very exciting, too. 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. Was this section created for you and your research, or did you inherit it from someone else?

Wong-Staal: It was an inheritance from David Gillespie, the man I mentioned earlier. He was chief of--I don't recall if the section had the exact same title, but certainly it was a section related to molecular biology. After he left, I was acting chief for a while, but in '82 I was formally named section chief.

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

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

Wong-Staal: Riccardo Dalla-Favera [Riccardo Dalla-Favera M.D.] was one. He's done really well. He's a full professor at Columbia now. He's the first one to show *myc* gene amplification in primary leukemia cells. Veffa Franchini [Genoveffa Franchini, M.D.] was working with me on mapping the *fos* gene from the feline sarcoma virus. In fact, we published one of the first papers on showing that the cellular counterpart of this gene had intervening sequences (introns). Now it's obvious, but at that time, it was a new concept. We were the first to characterize the *sis* gene for the simian sarcoma virus transforming gene. In fact, I think we named the gene *sis*. That was in our first paper looking at that. I think Ricardo was involved in that too, as was Steven Josephs [Steven Josephs, Ph.D.]. Steven 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 a scientist at, I think, Baxter Pharmaceutical Company.

Hannaway: Do you recall the debate over whether human retroviruses existed?

Wong-Staal: Yes. At that time, the dogma was that they did not exist. Most of the retrovirus work was done in the murine system and in the avian system, where there are very high levels of virus replication. At the same time, people who were looking for human retroviruses had some mishaps. I

mean that there were a few so-called discoveries that turned out to be contaminations, artifacts, whatever. This soured people on the concept that human retroviruses even existed. If they existed, then it should have been easy or obvious to find them by now. Even the really well-respected scientists--particularly the well-respected scientists--were very strongly against the idea that human retroviruses existed, with a few exceptions, and I think Bob is one of the few exceptions. He very strongly believed that they did exist.

And around that time, the model of the bovine leukemia virus [BLV] came about. Arsene Burny [Arsene Burny, Ph.D.], who worked on the system, happened to be a very good friend of Bob's, and he had a hard time isolating BLV from tumor tissues. It was found that the virus replicates at very low level. So Bob then said, "Look, here's a model in which you don't necessarily have very high titer retrovirus, so there may be exceptions and maybe humans are more like the cow than the mouse." I think that's the sort of thing that kept him going.

Hannaway: What convinced you that human retroviruses existed?

Wong-Staal: It was more or less along the same line. I mean, it's hardly conceivable that humans should be that much different from animals. 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.

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

Wong-Staal: Yes. The discovery or the breakthrough that led to the discovery of HTLV-1 was the discovery of T-cell growth factor, what is now called IL-2 [interleukin 2]. And what preceded that was the presumed finding of so-called HL-23 virus. I mean, that was supposedly a virus isolated from leukemic patients. I mean, it's still not clear whether there was ever a real virus. Certainly, in the early days, they detected reverse transcriptase activity, and it looked real. But subsequently, that virus was not growing well. It became highly replicative, and then it turned out that it was artifact contamination. I shouldn't say contamination. When they tried to go back to re-isolate, they ran out of factors that supported the leukemia cells. That really led 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 T-cell growth factor, IL-2.

Once they had the growth factor, then they were able to grow cells particularly from T-cell leukemias. The first patient, I think, had

cutaneous T-cell lymphoma or leukemia. Using IL-2 to culture those cells over the long term, they were then able to isolate the virus. And, still, they did not see a high-level replication, so on top of the long-term culture requirement, they also needed 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, PA, where it was disclosed that the first Gallo retrovirus was a contaminate? Do you remember this?

Wong-Staal: Right.

Harden: The question has never 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: Do you have any thoughts on this, just out of curiosity?

Wong-Staal: Well, who knows? I mean, do you understand human nature? I think some people enjoy seeing other people crucified in public. Right?

Harden: Yes, they do. That's what I'm getting at. So you think it was a vindictive act?

Wong-Staal: Yes. Bob polarizes people. There are people who are very close to him and supportive of him, but there are also people who are very antagonistic.

Harden: So I'm not missing some scientific nuance. It was a more personal attack to let it happen in public?

Wong-Staal: Yes, I think so. I think it was a set-up to humiliate him.

Harden: Now let's move into AIDS and get some chronology here. The first Gottlieb [Michael Gottlieb, M.D.] publication was in June 1981, and you became the section chief in '82. And, as I recall, Jim Curran [James Curran, M.D.] came to NIIH from the CDC to make a presentation to the National Cancer Advisory Board, where he saw Bob Gallo and urged him to begin a research program to identify the AIDS virus. This was in August or September of '82. So this is where we're going.

But let's back up now. 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 was probably around the same time. We had M.D.s in the lab, Ed Gelman [Edward P. Gelman, M.D.], for example. The physicians go to meetings, clinical meetings, and in the case of AIDS, they came back and said, “This is a very interesting new disease that’s going around right now,” and so on. I think that’s when we first heard about it.

We began to think more about the disease, based on the experience with HTLV and also based on the experience with feline leukemia virus [FeLV], particularly. HTLV and FeLV can cause leukemia, but at the same time they can also cause cytopenia. And what seemed clear after the typing of the disease in AIDS, was that it was the T cell that was in trouble. It was getting depleted. So because the tropism of HTLV is so specific for T cells, the same kind of cell that’s being depleted, you sort of have the yin and yang phenomenon. On one side you have abnormal proliferation, and on the other side you have depletion. It raised the possibility that AIDS was caused by a retrovirus. I think that particularly Bob was convinced that the cause of AIDS “smelled” just like a retrovirus. And then, because of the tropism for T cells, he and others think that it could be caused by a virus related to 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 what turns out to be a worldwide pandemic of a human retrovirus disease immediately thereafter?

Wong-Staal: Well, it may be. But, on the other hand, the discovery of the first human retrovirus, HTLV-1, also broke the barrier of credibility. Right? I mean, before, people would not have even entertained the idea that a retrovirus could be involved. But the fact that a human retrovirus that targets particular T cells had been identified made a retrovirus as the possible cause of AIDS more plausible.

Harden: In September 1981, NCI sponsored a conference on opportunistic infections and Kaposi's sarcoma. 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: No, I don't recall that meeting.

Hannaway: When did you begin to work on AIDS?

Wong-Staal: I would say in late 1983, early 1984, when my section was looking at samples, trying to detect sequences homologous to HTLV. But that was only a part of our program. The other part was to continue on with our work on HTLV-1 and oncogenes. With respect to the AIDS work, we got a couple of samples from France.

Hannaway: Is this Monsieur Shaddon?

Wong-Staal: Chermann?

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

Wong-Staal: Oh, the Shaddon virus.

Hannaway: Yes.

Wong-Staal: I was thinking of the Montagnier [Luc Montagnier, Ph.D.] group. But that sample came from a different source. The Shaddon sample came from Leibowitch [Jacques Leibowitch, M.D.], who was a member of a different French group.

Hannaway: Yes.

Wong-Staal: My group looked at the samples from Montagnier's group to see if there was any homology between HTLV, HTLV-1 and that virus. But as it turned out, we couldn't find any. There was nothing in there that we could detect.

But the Shaddon sample came from an AIDS patient. We ended up cloning HTLV from him. He turned out to be doubly infected, with HIV and with HTLV.

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

Wong-Staal: Yes, but that was a confusing part of the process.

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

Wong-Staal: 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: Looking back, there wasn't a lot of concern about biosafety. I mean, people would say, "Well, we're careful," as if same precaution one used for hepatitis work was adequate. They would work in the hood and so on. But certainly there was no BL-3 [biosafety level 3]. Things like that didn't even exist. In general, you used aseptic technique tissue culture

procedures, you work in a hood, you glove and gown. But other than that, I don't think there were additional precautions.

Harden: You didn't have folks in your lab who were afraid to work on this disease, then?

Wong-Staal: No. Now, my lab was a molecular lab. If we know that you get AIDS from blood or tissues, we immediately dump in SDS, phenol extract, so you really get rid of any possibility of infection, infectious material, right away. We're not really working so much with high-risk material. We're working with naked DNA or RNA [deoxyribonucleic acid]. That is not very infectious.

Hannaway: We'd like you to describe 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: Yes, I think that's true because it was a new virus. But not only was it a new virus, it was a very interesting and complicated virus. That meant that there were a lot of discoveries to be made. The new, transactivator

genes were one example. Every gene provided a new paradigm for a virus-host interaction. That time was a very productive period. It was dizzying, you know, because there was so much to do. You don't even know what to do first. I would say that those years were the highlight of my career, that period of discovery, intense discovery. I should mention that the most actively involved people in my group at that time were Beatrice [Beatrice Hahn, M.D.], George [George Shaw, M.D.], Sasha [Suresh Arya, Ph.D.], Mandy [Amanda Fisher, Ph.D.], Lee [Lee Ratner, M.D.] and Mark [Mark Feinberg, Ph.D.]. It was a fantastic team.

Harden: One of the first things that you did in 1984 was to clone and characterize the AIDS virus. Now, Mal Martin [Malcolm A. Martin, M.D.] was doing similar work, and in 1986 he published a similar paper. Can you tell me how the work of the two labs were different, or were they just repeating each other?

Wong-Staal: Mal Martin's work came much later than ours. 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 Mal published later. And then with publishing the viral sequence, it was the same three groups that first published the sequence: our group, the French, and Jay Levy's [Jay A. Levy, M.D.] group.

Harden: Was that done before the question of priority in discovering the virus arose? I ask because Dr. Martin apparently was the person who said the French and American viruses were identical.

Wong-Staal: Oh, we did that before the priority question arose. It was from the viral sequence that the two viruses were shown to be identical. We published the entire sequence, and the French group published the entire sequence, and the San Francisco group published the entire sequence. And then, in fact, we submitted 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 French isolate seem much more related than the San Francisco isolate.

We were thinking about the spectrum of relatedness. I mean, if you look at HIV, you really have a whole spectrum, some of them more closely related than others. It depends on what end of the spectrum you look at. So the question that Mal took issue with was whether the similarity of the French isolate and the isolate that we sequenced could be justified on the basis of strain-to-strain variation or where there was too much to be expected from that.

There was really no point of reference, because if you look at HTLV-1, 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 there were no guidelines, in other words. But as more isolates were sequenced, of course, we saw more of a pattern of how much variation usually exists among different isolates.

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

Wong-Staal: Yes, obviously. But, on the other hand, however, I should point out, that it was 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 were divergent. One of them was the isolate called RF, and it's used extensively now because it is viewed now as a prototype that's different from the 3B isolate and LEI isolate that were available in the early days. So RF 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 was sort of a stroke of fate that we used the 3B virus for sequencing and analysis.

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," 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. Vp just means viral protein, so this was the gene that coded for viral protein r, which became *vpr*.

Harden: Would you elaborate a bit on this? In this publication it is described as an accessory gene. What does it do? Tell us about discovering the gene and learning about it.

Wong-Staal: Right. At the time, we discovered it as an open reading frame, i.e. a stretch of nucleotide sequence uninterrupted by stop codons . In other words, it has the potential of coding for a protein. From the sequence, it was hard to tell more because it was a very short sequence, smaller than most genes that we’re used to. But what that paper described is that we could actually show that that sequence is expressed into a protein and that patients who are infected actually make antibody against that protein.

At the time, we called it an accessory gene, function unknown, because it didn’t seem to be critical for virus replication, at least not in T-cell lines that people usually used in the laboratory, because if you

removed that gene by deletion, the virus seemed to do just fine. It was very puzzling.

It turned out to be a very interesting gene. It had unique properties. One of the unique properties of HIV is that it can infect a cell that is resting, not actively dividing. 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, could not infect such cells. They need cell division to do it. Those viruses were stuck because they could not get into the cell's nucleus. Their viral RNA/DNA complex could not penetrate the nucleus unless there was cell division, because that is when the nuclear membrane dissolves.

It has now been shown that *vpr* plays a critical role in allowing the virus to get into the nucleus in non-dividing cells, across an intact nuclear membrane. It is critical. If you delete that gene, the virus can do well infecting T cells, but its ability to infect macrophages is very much impaired.

And then there's another effect of *vpr* on inducing cell cycle arrest in G2. So from a biology point of view, the *vpr* gene is very interesting. It is a highly conserved gene, which made it clear that it played an important role in the virus's biology and pathogenesis.

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. From the early isolations and sequencing by different groups, it was clear that HIV is not a single genetic entity, that there is 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 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. That kind of phenomenon has been described for other RNA [ribonucleic acid] 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. Our observation at the genetic molecular level corroborated studies from other scientists in terms of virus neutralization that very often is type specific--an antibody from one patient that may neutralize its own virus may not neutralize other virus isolates. But, furthermore, within the same patient, neutralizing antibody against an earlier isolate may not neutralize a later isolate. This, again,

suggests antigenic drift. Our description was at the molecular level. Other people had immunological data.

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

Wong-Staal: Yes, correct.

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: I think the biggest change with AIDS was that suddenly, the research that we did caught the attention of the public, because prior to that, no one cared about oncogenes, particularly if it was a yeast gene or a regulatory mechanism, etc. I think that was both good and bad. I think the good part of it was that even though what we were doing was very basic—we were looking at fundamental gene regulation and structure—suddenly it had a relevance for something important, an important disease. But the negative part was that we were under the microscope all the time, and people had

undue expectations. The pressure was always on. When will there be a cure? When will there be a vaccine? What's next? And that part of it sometimes could be too much.

In terms of the funding, at the time at NIH, it wasn't too much of a problem. We were getting good support and I think it was justified because of all the progress that was being made. Even outside the NIH intramural program, AIDS research was supported. But that led to the perception that if you labelled your research as "AIDS research," you could get grant money. So I think there was also a lot of abuse of the system, that people who were not really working on AIDS labelled their research as related to AIDS and so got money. As a result, trying to get AIDS money became very competitive because you had so many people coming in. At that point, I don't think it was a particular advantage in obtaining grants to say that you were working on AIDS.

Hannaway: We are also interested in the effect of all of the publicity and debate over who discovered AIDS on the working of the Gallo lab. Particularly, we want to know if 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, we hardly thought of patenting one's work because, our interest was in scientific discovery and gaining new knowledge, but not the

commercial implications. With HIV, the diagnostic test was based on our basic science work. We were actually told by officers from the Institute Director that we should file for a patent because AIDS was an important public health problem, and in order to attract pharmaceutical companies to make a diagnostic test, we really needed patent protection for our discovery. Because of the commercial issue, other aspects of profits and rights and shares of equity, royalty, whatever, had to be dealt with, and that, I think, escalated the problem tremendously.

Harden: The first patents for the ELISA test for AIDS came before passage of the 1986 Technology Transfer Act that required federal scientists to submit discoveries with potential commercial application for patenting by the government. So, you all were getting instruction then from the administration that you should pursue a patent on the test. Did this put some pressure on you, not only the thought about profit but also about sharing samples, sharing information, whose name went on which paper, etc.?

Wong-Staal: Exactly.

Harden: Was there a lot of conversation about this within the lab, among the investigators themselves? Did you all talk about it and sit down formally and discuss it, or talk about it informally?

Wong-Staal: There was not so much discussion at our level as researchers. The most critical patent was the blood test. With respect to that, I was not involved. Subsequent to that, we just patented everything and we included everybody in our patents--I mean, the people who worked on the project. I also have to say that we didn't have the best patent lawyers at NIH, so I don't know whether later discoveries ever resulted in patents.

Harden: Let's go back to the question about the controversy over who discovered the AIDS virus.

Wong-Staal: As I said, there was no question that Montagnier's group first had the right virus, although what they published was not convincing and was only from a single patient. Our laboratory had multiple isolates from different patients. Multiple isolates made a much stronger case for etiology. And repeating what I said earlier, I think it was unfortunate that we had focused on this one isolate that seemed to grow the best. As it turned out, the reason it grew so well is because it was a contaminant that took over. It was the first prototype that we analyzed and patented. It produced the cells used for the blood test patent. But a lot of people are not aware that contamination didn't happen only in our lab. In fact, it happened in Montagnier's own lab, because when they went back and sequenced the early samples, their earliest LAI isolate was not the same as what was

subsequently defined as LAI. They had contaminated their own cell line with a more replicative virus. That happened also in Robin Weiss's lab. I mean, Robin Weiss [Robert Anthony Weiss, M.D.] in England published the first British isolate of HIV. In fact, we got samples from him. Turned out to be the same virus. So this viral isolate happened to be a very highly replicating virus and that it easily contaminated other cultures. The thing to stress is that there was more than one isolate in Gallo's lab, that we could have chosen any one of those to expand our studies on.

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 in France being seen as a hero? Was it Gallo's personality, the fact that you said he polarizes people, or is there some other reason?

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

Harden: Or could it be the fact that he works for the U.S. government?

Wong-Staal: I'm not sure it's that. I think that Americans have a different mentality from Europeans. I know of no scientist, whether European or American, who really respects Montagnier as a scientist. He's not a good scientist. I can say that on tape. And yet the Europeans rally around him. They protect him, they want to push him as the discoverer. But Americans want

to destroy their own heroes. 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 in which Bob does science. He's very aggressive. Sometimes, if other groups make a discovery, he might say, "Why couldn't we have done that first or thought of that first?" I have even thought, "Bob, let other people do something first. We don't have to make all the discoveries and do everything first." But he does have this attitude that the lab's goal is to win, 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: He's not the only scientist that's being persecuted either. 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 virologists interacted, the way different labs, interacted. They would routinely send each other samples and tell each other of their findings in informal ways. And this aspect of the culture of virology is not understood in general.

Wong-Staal: Right, right, right.

Harden: And I think that there is also an assumption that scientists working on medical research should have the demeanors of TV characters like Marcus Welby, to want to hold people's hands and comfort them. In this view, the intellectual give and take and the personal goals for achievement are not considered important. When someone is strong enough to let that show that he wants to achieve. . . .

Wong-Staal: Well, they're human.

Harden: They're human, yes, and the condemnation of some parts of society may come down on them because of it.

Let's broaden the discussion a little bit here and ask if you will talk about what kind of interaction you saw on the NIH campus among the various institutes working on AIDS, especially NCI and NIAID [National Institute of Allergy and Infectious Diseases]. Were there NIAID people collaborating with you, for example?

Wong-Staal: We were collaborating with Warner Greene [Warner Greene, M.D., Ph.D.], but I think he was in NCI, not NIAID. Mostly on HTLV rather than HIV. We certainly gave reagents to NIAID people.

Harden: Were you going to the same seminars?

Wong-Staal: Oh, definitely, yes. Especially in the beginning, yes. Gallo has this annual lab meeting that was open to other people at NIH. I think a lot of Tony Fauci's [Anthony S. Fauci, M.D.] people came, for example.

Harden: What about interactions in the Clinical Center? We interviewed Sam Broder [Samuel Broder, M.D., Ph.D.]. He talked about being able to see a patient today, get the latest results from your lab, and then try to use that knowledge in the clinic.

Wong-Staal: Oh, yes. I forgot about Sam. I think Sam Broder was very close to the lab. He was involved in trying to treat HIV infection. We had a close interaction there.

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

Wong-Staal: There may have been some, but I think in the early days, our lab so dominated the field that there wasn't any attempt by any other lab to take that away from us. It was more a collaboration situation, I would say. For example, Broder's expertise and interest was complementary to ours rather than competitive. And the same thing with Tony. I mean, he was more involved in the immunological aspects of AIDS, and certainly we were not immunologists, so it was more a productive interaction.

Harden: So in your view, the different labs looked at the AIDS problem from their own area of expertise?

Wong-Staal: Yes, exactly.

Harden: And you think that this was the most productive way to go?

Wong-Staal: Yes, because to study HIV, you really needed a multidisciplinary approach, and it was 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. 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 were particularly slow in responding, certainly not at the laboratory level. We did the best we could, and I believe we were getting support from the institutes. Perhaps they were criticizing the second level of the problem, the translation of the discovery into implementation of diagnostics, etc.

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

Wong-Staal: No. I'm not saying that I don't think that was as effective. What I'm saying is that the activists' 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, yes. What we do in the laboratory is not immediately available to them anyway, and if they're infected, they're not interested in the diagnosis. They are 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, about all the Freedom of Information Act (FOIA) requests. I actually was very lucky because I left right at that time, at the beginning of 1990. I think the FOIA requests started, you know, in 1989, '90. So I wasn't really subjected to a lot of that. But I did have, of course, interaction and contacts and discussions with people who stayed behind, and I know it was very demoralizing, and it almost paralyzed the lab. I mean, it was really to the lab's great credit that it continued to make discoveries and progress because, as you might imagine, it was not only the mechanics of the process—to provide document upon document, which was all-consuming—but it also depressed the esprit de corps, the

spirit of the lab. No one wants to be criticized, to be looked at under the microscope. I think it was a really 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: I was on the task force that Gallo formed, but it was not really inter-institutional but rather international, because he was including a lot of scientists from Europe, including Chermann [Jean-Claude Chermann, Ph.D.] and Montagnier. He also included Leibowitch. There were people from all over the country participating, and from other countries too.

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

Wong-Staal: Well, it was actually an LTCB-organized task force [Laboratory of Tumor Cell Biology]. I don't think it had the mandate of the Cancer Institute. But Sam Broder certainly was a part of that, and he was the director of NCI.

Harden: We've asked the following question of everyone we interviewed and have received a variety of answers. Did you or your family 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, it was the contrary. I mean, when they found out I worked on AIDS, usually they were very interested. It was a good dinner conversation. They were curious about what's going on. I think, actually, I think people know that the virus is not that easily transmitted.

Harden: Even early on?

Wong-Staal: Oh, I see, you are asking about the very early days. I think maybe there were a couple of instances when people were wary. 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, "Are you sure it's safe?" and I explained to her that I protected myself 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 more hands-on activity in the laboratory?

Wong-Staal: I think it is fun to work in the lab. But it's also very frustrating because things only work part of the time. I think the euphoria is probably outweighed by the frustration. In that sense, I think being a group leader and having a group working with you is 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. I'm not experiencing the daily frustrations, but people actually come to me when they have something interesting, and then we discuss what should be done next. That part of it is a more positive experience. On the other hand, I don't feel like I make the discovery with my own hands. So it is a tradeoff, I would say. But I feel now, at this stage of my career, that I'm better at doing the overall direction than working at the bench. I know I can accomplish more this way than being hands-on.

Harden: The Gallo lab was very large, and when some problems arose with respect to various international questions, some people criticized the lab for being too large, saying 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 for the lab. 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 where you can have a research program as a group. I mean that there can exist a reasonably large group with a central mission to do something, and at the same time have a multidisciplinary approach within that large group so that the different sub-groups complement each other to achieve a defined goal. You can't do that in a university, because in the university, each lab is on its own. It has its own set of goals, and individual investigators sometimes collaborate, but they're not forming part of a whole program. I think it is tremendous that the NIH can have intramural programs like that.

But, of course, there are instances when you can't directly manage a group 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.

You can say that it's anti-individual because everyone is working as a group rather than as individuals on investigator-initiated research. But perhaps that's what NIH should be about, that you can have group efforts. People always talk about Manhattan Projects. I think that is like a

Manhattan Project when you have different groups working towards a common purpose as we did on AIDS.

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: We were the first to obtain a molecular clone, the first clone and then multiple clones to actually show that molecular clones have biological activity—that is, the clone depletes T cells in culture. That really proved that the virus was the agent, because 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 you see that the virus can do in tissue culture, using molecular clone—that is, there's no other genetic information associated with it—what a candidate virus from a patient can do, I think it provides a stronger proof that this particular virus is the causative agent. So I think the so-called Koch's postulate should be put to rest.

We also were the first to describe the genetic diversity of HIV from different patients, both inter-patient and intra-patient. My group also first described the detection of HIV in the brain.

What else? There were all these genes. We actually were the first group to identify the *tat* and *rev* genes, which are the critical *trans*-activator genes for HIV expression. We also defined some of the mechanism and function of other regulatory genes.

Hannaway: In 1990, you were appointed to the Florence Riford chair in AIDS research at the University of California, San Diego [UCSD], and you left the National Cancer Institute. 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 was at a stage of my career where I felt that, much as I admire Bob as a leader and as a scientist, his visibility was really overshadowing me. I think we had complementary expertise, and people recognized that I was doing molecular biology and he was not. But still, I think the association sometimes worked against me. So I thought, "It's time for me to move." Also, part of it was because the Crewdson article [John Crewdson, "The Great AIDS Quest," *Chicago Tribune*, November 19, 1989] that came out and marked the beginning of all the Freedom of Information Act requests. So I thought, "I need to get out of here." I chose San Diego because I did a year's 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 is also Scripps [Scripps Research Institute] and Salk [Salk Institute

for Biological Studies] and, you know, the La Jolla Institute for Allergy and Immunology. It's a very rich scientific environment.

In terms of the differences in operation: First of all, really for the first time, I was completely my own boss, and that was very exciting. The ability to have students and young people is also very exciting. When I was at NIH, it was very difficult to have students. I had a couple of students, such as Steven Josephs, my technician who went to American University. But, it was very rare at NIH. At the time, most of the postdocs at NIH were hired only through the Fogarty Center, so you really only got foreign postdocs, and then the rest of the NIH staff were 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 at a university.

Of course, it's also a very different environment in that, now I have to worry about my financial situation, writing grant proposals and so on. That part of it is somewhat of a struggle. Especially in the beginning, I had to learn the process and transition from being in a protected NIH environment to securing my own funding. And it's not getting very much easier, I have to say. And then, in the beginning, I was not looking forward to having to teach, but now I'm beginning to enjoy it. I think it's good to have the interaction with students.

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: The Center program is from NIH, as you well know. It's sponsored by NIAID, at least at this time. Now I think they're bringing in other institutes as well. They wanted to establish different centers of excellence in AIDS research in different parts of the country. The idea was that if active research already existed in an institution, NIAID could provide the glue that pulled things together by providing for resources and administrative structure and so on. We put in an application, and we received one of 11 Center awards.

Separate from that, the university also wanted to start an AIDS research program, the equivalent of a department, but it would not be called a department. It was called an organized research unit. We refer to it as the AIDS Research Institute just to be different from the Center, because the Center may be a temporary thing. We were hoping that the AIDS Research Institute will be permanent. So the proposal went to the dean, and then it went through the regents, and it was approved. It is university wide. It's not just UCSD, but University of California and the whole UC system. I was named director of both the Center for AIDS Research and the AIDS Research Institute. It is a big challenge, but I think with all the basic and clinical research at the university, and in the region, it's necessary to have this structure here.

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. Since I moved to UCSD, I've become interested in gene therapy. It's a marriage of molecular biology and medicine. We actually have one of the earliest gene therapy trials for HIV patients in the country.

Harden: I want to show you two schematic diagrams. This one, Howard Temin [Howard M. Temin, Ph.D.] drew 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. In it, there are basically three points where it is obvious to intervene with the reverse transcriptase or the integrase or the protease inhibitors, in addition to the cell membrane at the point of infection.

Wong-Staal: Right.

Harden: Now, this second diagram is from one of your papers. [Poeschla, E.M. and Wong-Staal, F. Gene Therapy for HIV Disease. In AIDS Clinical Review, 1995, 1-45.]

Wong-Staal: Yes, I recognize it.

Harden: It has some similarities, but it's a lot more sophisticated. What I want you to do is tell me what we've learned between the two diagrams. What were people thinking in 1986 and what are people thinking now about ways to intervene?

Wong-Staal: Dr. Temin's scheme outlines the different steps for virus replication, and this implies that each of these steps can be interfered with. In my scheme, I'm actually putting down what strategies can be used to intervene in some of these processes.

Harden: In the paper, you walk readers through it.

Wong-Staal: Right. For example, I say here ribozymes and antisense can act at the time the virus comes in because the genomic information is RNA. Ribozymes recognize the specific RNA by sequence complementarity and then inactivate it by cleaving it. Antisense at the same time hybridizes the RNA genome and can prevent it from being utilized. The CD4 [cluster of differentiation 4] receptor acts as a competitor at the level of binding of the virus. Those would be strategies to stop the virus at the point of infection.

I draw this line there [points] because it 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 would not be making more progeny, more viruses. 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 progeny viruses.

We can also talk about TAR [Trans-Activation Response] decoys. I've mentioned that we discovered the gene *tat* [trans-activation of transcription], 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 a TAR decoy means that you express that RNA element as a decoy molecule, so it competes for the binding of the Tat protein, which pulls it away from its normal function. TAR decoys have been used, including by Gallo's lab, for virus inhibition. Next, let's talk about trans-dominant [a mutant form of the protein that effectively inhibits the function of the wild-type protein] Rev [regulator of expression] protein. We also did one of the earliest work demonstrating how it works in the cell. Gary Nabel [Gary J. Nabel, M.D., Ph.D.] 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 interferes with normal Rev function. Because Rev is critical for HIV replication, you can also inhibit virus that way.

An RRE [Rev Response Element] decoy is like the TAR decoy except now, instead of binding to Tat, it binds to Rev. It prevents Rev from working. The RRE decoy does not prevent transcription, but it

interferes with the nuclear transport of incompletely processed viral RNA and therefore utilization of a subset of the viral messenger RNA. It is post-transcription in its interference at that point.

You can also use other strategies like the trans-dominant Gag [Group antigens] protein as a mutant Gag protein that prevents the assembly of the virus. You can also have trans-dominant envelopes, and, finally, what I would call envelope traps. An envelope protein binds to CD4, so if you can express intracellular CD4, you can trap the envelope inside the cell. The alternative is to express an antibody to the envelope protein, an intracellular single-chain antibody. It binds the virus envelope inside the cell so that it is not free to become incorporated as a new virus is formed.

Harden: So with all these different ways to attack the virus, how come it hasn't yet been inactivated?

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

Harden: I believe there was something in this week's *Science*, or another recent issue, about naked DNA, plasma DNA, that seems to look very promising.

Wong-Staal: Yes, yes. But that is a strategy to use gene therapy for vaccination, to stimulate the immune response.

Harden: Rather than a therapy approach.

Wong-Staal: Right. What we're doing here is trying to inhibit the virus rather than to stimulate the immunity. For stimulating immunity, you just need to get a gene into a cell that will have some level of expression of that protein. But to inhibit the virus, we have to get the gene into a significant number of the functional target cells.

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

Wong-Staal: These approaches are all sort of equivalent. We prefer the ribozyme for a number of reasons: because it works with RNA; it's not immunogenic; it's not tied to a single gene, that is, you can design a ribozyme to match any part of the virus genome. We can have a dozen different ribozymes that recognize different parts of HIV and attack it. 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 by blocking the protein expressed by one gene for the same reason. With ribozymes, aren't limited to one gene, you have many ribozymes targeting many different viral genes that you can link together because they will be transcribed into separate small RNA molecules. 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 your approach ready to move into clinical trials? You said that you've had one clinical trial.

Wong-Staal: Yes. We have introduced a gene 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, 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 to compare the two populations in the patient to see if the ribozyme is doing its job. If it is, the cells would not be infected by HIV, and therefore they should persist longer than the control population of cells which can be infected and killed. Our goal is just to see if the ribozyme gene is functional in that sense.

We were not working under optimal conditions because our vector 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's population of cells. So that's the first part. The second part is to increase the efficiency of gene transfer. Right now, because of the vector's low 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, especially for developing countries. You can never do it on a large scale in countries that don't have the necessary laboratory expertise, but those countries are where the greatest impact of the epidemic is. So we're working on getting vectors that can be directly injected into the patient to deliver the gene. And, ironically, I think that perhaps the best vector to do that is HIV itself, if you can turn HIV into a vector for delivering the gene that would kill itself.

Harden: That is indeed ironic, isn't it?

Wong-Staal: Yes. It's sort of poetic justice.

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

Wong-Staal: That's true. But the pace of discovery is slower now. In the early years of the epidemic, everything we did was discovery. Right now it's more challenging, but it's no less exciting.

Hannaway: You've mentioned the annual Gallo laboratory meeting on AIDS. Do you continue to participate in that?

Wong-Staal: Yes.

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 somewhat about collaborating.

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

Wong-Staal: Yes. So far, they have not had a major program on gene therapy. They're more interested in cytokines, chemokines, the small-molecule approach. Which is okay, you know. I don't need the competition. There's enough competition.

Hannaway: Do you have any collaboration with David Ho's [David D. Ho, M.D.] group in New York?

Wong-Staal: We've had some, off and on in the past, but not really that much. Again, we have taken different directions.

Harden: I'd like to ask you one question that 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, even after HTLV-1, there was a lot of resistance to thinking that this new disease was a retrovirally transmitted disease. I mean, there were theories of antigen overload and whatever else for a long time. I think mentally, they would not make the connection, at least not as readily. Also, the technology for growing T cells was not there, so

Harden: T cells were not even there—that is, in 1955, there was no ability to subdivide white cells.

Wong-Staal: Right, exactly. The ability to isolate the virus was not available. Reverse transcriptase was not there. 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.

Hannaway: Epidemiologists might have some understanding of how it was transmitted.

Wong-Staal: Right. That's true.

Harden: And they would probably have figured out that the disease was sexually transmitted, blood-borne.

Wong-Staal: Right. So they might have taken action from a prevention point of view. But by then, many people would have been infected.

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? What I'm getting at is the question: 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, there is work on linking some of the decoys, what they call aptamers [oligonucleotide or peptide molecules that bind to a specific target molecule], for interfering with *tat* and *rev* and so on. The problem with HIV is really, as Tony Fauci's recent studies have

shown, is that a person who's infected probably needs to be treated forever. The virus, once it's established itself in the immunological reservoir, can never be completely eliminated. Anytime you withdraw drugs, the virus comes back. So you have to treat the patient for two or three decades or longer. And to maintain a drug at that high a level for such a long time, there are problems. First of all, you can have cumulative toxicity. There is also the problem of resistance. That's why you also need not just one drug but three or four drugs. You also need to mix the regimen. This is very difficult, I think. There are also 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 very difficult with a small drug approach. That's why I personally came to gene therapy. You need something that's 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, 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: How would you advise policymakers to think about this? They have to deal with constituents who are ill and constituents who don't want to spend too much money on open-ended research. 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: 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. From this model, this system, we gained a lot of insights into basic molecular biology and virology and immunology. So it was not all just practical. You have to think of AIDS research as a window of opportunity. This is one of a few major diseases for which we have a defined cause. For a lot of the cancers, we still don't know what causes them. But with AIDS you know that the virus causes it, and if you can stop the virus, you can stop the disease. It's a defined target even though it's a very slippery target. We shouldn't lose sight of that.

And the second part of that is that the victims of AIDS are usually young, productive people, and because of that, we are losing a lot economically. This alone should be a strong motivation for policy makers to fund the effort to keep AIDS under control. Hopefully, they won't need to make the investment forever. Up to a point, putting more money into AIDS research may not make the process faster because there's only so much one can try at the same time to see what works. A more coordinated,

rational approach is more important than the trial-and-error type of approach.

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

Wong-Staal: Yes. The other part, of course, the vaccine program, is very important because prevention ultimately would be the most effective means of stopping the epidemic. I'm still having trouble understanding why public health education is not working as well as we hoped. It has worked to some extent, I guess, but it's not the final answer. But a vaccine would halt the epidemic. But we also shouldn't be under the impression that a vaccine is all we have to worry about, that therapy is solved. Therapy is not solved.

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: We have just been evaluating each lab within NIAID rather than taking a global policy approach. 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 can be

more coordination in some parts of the institute. But overall there's good coordination.

Harden: Is there anything else, from start to finish, that you can 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 want to thank you very much for speaking with us.

Wong-Staal: You are welcome.