And so what are you doing with yourself right now?

I'm a professor at NYU, and I manage the -- direct the research of this new Center for Urban Science and Progress.

Larry, I got all your levels. I'm ready and I'm rolling.

Okay, please roll on.

Cool. Well, it's -- we're glad to have you back on this coast anyway, although California's nice, but --

Well, I'm no longer in California. I mean, I still do part time for -- a little bit part time for Craig, for Craig, but I haven't been, in fact, out to San Diego for over a year.

Got you. Well, so we're rolling, so we'll start the interview now. So --

All right.

-- and I'm going to ask you the hardest question first. What is your name and how do you spell it?

My name is Ari Patrinos. A-R-I P-A-T-R-I-N-O-S.

Cool. And I guess we can -- we're going to get in the way back machine and go back to your DOE days, and let's start with -- and Christopher and I will sort of bounce it back and forth as we go along. But as you know, I'm kind of a big mouth, so you just, you know, tolerate me as best you can.

He's also my bouncer --

[laughs]

-- which is very nice of him.

More than happy to do that.

Yeah. [laughs] Cool. So let's go back to the beginning, and how was it that the Department of Energy, of all places, you know, got interested in the genetic code?

Of course, have never answered that question before. [laughs]

No, I'm sure not, or with any sense of irony.

[laughter]

So the Department of Energy is the successor of the Atomic Energy Commission that was born in the dawn of the atomic era. And with the promise of nuclear energy that was sort of the positive side of the nuclear weapons that we exploded in Nagasaki and Hiroshima came also additional concerns about whether indeed it would have been -- it would be such a cheap energy to -- too cheap to meter energy, and it had all these other tremendous benefits. But even back in the early days, there was concern that radiation, even if properly harnessed for the production of electricity, could have some deleterious effects.

And so at that time, and, in fact, in 1947, the Atomic Energy Commission set up a department or a division that looked at biological research. And it was biological research to understand the effects of ionizing radiation on human biology. That was the objective.

And so it started some pioneering work back then, and some of it was horrible with today's standards, you know. It was the time when people got irradiated because -- some of them were terminal, for example. And people were volunteering to have their -- themselves be guinea pigs just to look at radiation. Some of it was unethical medical practices of trying to see whether radiation could do something about curing cancer and -- so a lot of that was with today's standards horrible, but with those standards back then, perhaps understandable.

Most of the work, however, dealt with radiating animals, whether it was rats, or beagles, believe it or not, or other animals. That was a lot of the bulk of the work. And the hope was that by doing these studies, you would find impacts on the human -- on the human biology. And guess what? It turned out that that's not the case. So, a lot of the results didn't lead into insights, and so there were frustrating years of research that we got a lot of observations but not a lot of meaningful insights.

So it was back then, in fact, that some of the ideas that until we got into genetics -- there was already an understanding that radiation would be damage the system -- the genetic system. Unless we got into it, we would never be able to really understand how radiation impacts human biology.

So the notion was, by that time, we knew about the human genome, we knew roughly how big it was, and why don't we sequence the human genome? And as a result, we would, in fact, find the impacts.

It turns out, however, this coincided with the time when there was a -- the beginning of a reduction in the work in the national labs dealing with nuclear weapons. So there was some anxiety, as always happens in cases like this, among politicians, especially prominent senators in

the key states where a lot of these people are employed about what we're going to do with these very smart people, you know, when we start phasing down work in nuclear weapons? And at the time, and just as it still is to a large extent but hopefully changing, the people dominating science management in this country, and practically everywhere, were physicists. And there was, especially at that time, a very different philosophy about the approaches to scientific research between physicists and, let's say, life scientists.

The former were perfectly comfortable asking for huge amounts of money to do discovery-type research, you know, smash particles together and see what happens and ask for billions of dollars. I mean, it didn't -- the latter, I mean, the life scientists were still into the small science -- and I don't mean it in any derogatory way -- hypothesis-driven. You know, the notion that you would just acquire a bunch of data and something will come of it was alien; probably still is for the bulk of biologists.

So it was, in some respect, natural for that community of physicists, even though in their bosom were a few of us who were more in the life sciences, environmental sciences. But they were dominating, just like they still dominate in the Department of Energy, the running of the scientific enterprise there. So it was natural for them to be the ones that had this audacious proposal. "Why don't we sequence the damn thing?" And, "Well, how much will it cost?" Well, at that time, we said it was $10 a base pair. Well, maybe we'll get it down to a, you know, a dollar, you know, if we invest some initial money. So what is it? It was about $3 billion. Nothing. That's, you know, change for physicists.

So it was the combination: the time had come, the notion -- the idea was smart. Had the backing of the science managers at the top, physicists who thought maybe this was another opportunity to do big science. And then you had the powerful senators in states like New Mexico, where we had Los Alamos and Peta [spelled phonetically] managing specifically -- there was many -- who had an interest also in medical research, mostly on the neurological problems, because he had children who had problems of that kind. So it was all the right stars were sort of favorably aligned for that idea to become fertile, you know, to fall on -- to that seed to fall on fertile grounds in the Department of Energy.

One of my predecessors in DOE, Charles DeLisi, very, very insightful, very smart guy, had started as a physicist but was a biologist, in fact had worked at NIH; his boss at the time, Al Trivelpiece, who became eventually the director of Oakridge National Laboratory; and then Pete Domenici, again, it's usually people that make these things happen, the right people at the right time at the right place, so --

Who articulated the idea initially? Who said it first? Was it Dr. DeLisi?

Yes. I have a memo from DeLisi that was written 1985, where he outlines, in a 14-page memo, his vision about the Human Genome Project. And, you know, it makes your skin crawl because if you read it now, he predicted practically everything, including the interest of the private sector. He didn't quite predict that it would be this race between the two, and -- but he predicted a significant interest on the private sector. It really is. And he predicted that significant investments would trigger research in proving the technologies for sequencing. He was

primarily a bioinformaticist, so he predicted the rise and the prominence of bioinformatics, and how borrowing from the physical sciences, a lot of these activities would greatly benefit, you know, a lot of the research that was done for other purposes, whether it's weapons or other industrial applications, you could steal some of these, as we did, as it so happened.

So it was Charles DeLisi's vision, and his insistence, and, I think, his initiative. I give him tremendous credit for that. And he was appropriately honored by President Lincoln with the -- Lincoln -- Clinton --

[laughs] Same guy.

-- with the Citizen's Award. He hopes.

Yeah. Wishes.

[unintelligible]

Yeah. The -- so, I was a reporter in those days, and I came out to the Santa Fe meetings that were sort of the early planning sessions about, well, if we really do this, how do we do that? Well, what did it take, you know, to go from a 14-page memo -- and even with Pete Domenici's support -- I mean, he's one senator in the hundred. What was it that sparked the imagination or Congress's -- created Congress's willingness to do this or push this into having some -- moving from an idea to something with momentum that was really on its way to becoming a program?

I was already in the office at the time. In fact, ironically, I was leading an initiative that was competing with the genome initiative at the time. It was the Global Change Research -- Global Climate Change. And we knew that there were -- it would be very difficult to have two initiatives out of the same office. And it was, frankly, through my competition with the genome project where eventually I was, in fact, seduced and crossed to the other side [laughs] as a result of that knowledge. But I followed it very, very closely.

It took, I think, some brave moves by a few people. I mean, Charles DeLisi went to his boss and asked for reprogramming. That was in 1984, '85. And I don't know how it is anymore, but I don't suspect it's any easier than it was back then. To reprogram something that has already been appropriated, you know, by Congress, and signed by the president, and therefore is in law, in a statute, requires another act of Congress. You have to go in with a specific proposal, and you have to haggle with usually some junior staffer that really wants to give you a hard time because they don't want to change anything and they want to push you back on it.

So it took some give-and-take. And it wasn't a lot of money. It was back then, maybe a million or $2 million. All that would have been required primarily is to hire a couple of people, run a few workshops. And -- but it was a difficult move. Contrast that to the initiative that I was pushing at the time, that I had already gotten some money. So we thought we had the leg up on

this particular initiative. But it was quickly -- as I said, I was so quickly seduced. It was the, you know, the simplicity of it, the elegance, the ease to explain. You know, it was fascinating.

It didn't take much eventually to get the couple of million dollars. And once you got a couple of million dollars and you had the captive labs that you -- worked for you, and, of course, they were salivating with the opportunities that were obvious to some, especially since some of them were key scientists that had contributed ideas and had, you know, had exchanges with DeLisi and the other folks in the office. And I have to give tremendous credit to Dave Smith, who is the division director, eventually, for the life sciences, and also worked for me for a short time when I followed Gallus [spelled phonetically] who followed DeLisi at that particular job, and people like Marv Frazier, who was with me to the end of the Human Genome Project. They were the people that in the many respects did the heavy lifting of writing the documents, translating the documents into bureaucratese so they could be easily sold. You know, the day-to-day activities of putting together the workshops, inviting the right people; all of this work that sometimes doesn't get praised, doesn't get recognized.

But it's need for it to actually happen?

Yep.

So we -- you know, the famous -- I'm going to ask one more question. I'll let you in here. So the thing I was always fascinating to me -- and I talked to Jim Wyngaarden about this, you know, back when in 2003, actually, when we -- when the Genome Project was completed, and, you know, so you guys are -- have this idea. You're starting to put resources behind it, and you have a lab to work, all under the Department of Energy. And it's now getting some newspaper attention, some media attention. It has the support of some powerful senators who are pushing this.

Over here in Bethesda, the sleepy organization that's been used to the garage kind of approach to, you know, one guy working on a bench, you know, on an idea kind of approach, suddenly sees that there's something happening, and it's in their sort of sweet spot of their research in genetics, given GMS's general activity. How did that -- what -- how did they begin to respond to, and could you describe sort of the -- you know, they couldn't commit and just compete directly. They had to figure out how to collaborate with this other federal agency. How did that internessing struggle go?

So, it wasn't pretty from several sides. And, you know, what I'm going to say is a bit controversial, but, you know, I believe it, and I'm stage of my life and career where I can say it.

So there was a lot of medical research and biological research done in the Department of Energy and Department of Energy labs for many years before the human genome. But what had happened, quite honestly, is that quality of that research had deteriorated, as is to be expected, because DOE and the DOE labs in the areas of medical research and biological research were fat and happy. The funding was always adequate, and I think the quality suffered because there

wasn't much competition, and there was a tendency to isolate themselves from the much broader scientific community in those issues. And it wasn't universal. I mean, there were very good people in the lab, goodness [spelled phonetically] Charles DeLisi that came out of Los Alamos.

But in general, by the time, especially that, you know, David Gallus, my immediate predecessor, and I took over, we -- it was clear to us that the quality had dropped, again, because of non-sufficient competition, isolation, and, you know, if there was criticism, for example, by the mainstream biological community, some people in the labs, and they say, "Well, we don't need that community. We got adequate funding. Our funding is guaranteed, so I don't really care what they think about our quality," which is, you know, certainly the wrong attitude to take.

So there was also, on the part of the NIH community representing the mainstream biological sciences community, a certain jealousy. It's this envy about how fat and happy the DOE labs had been in biology, and a certain resentment because here we had to really suffer for the pennies that we get. And these guys in these ivory towers, you know, in the labs are getting multiple millions of dollars, and they don't have to answer for it as much as we have to answer for it.

So there was a natural, I would say, enmity, you know, envy -- I mean, it was a -- and it was as always happens in cases like this, once communities are isolated or not sufficiently interacting, they develop their own cultures, they get their own meetings. You know, they start believing their own propaganda on all sides. And, you know, so, in many ways, it was understandable that there were a lot of people at NIH worried when they saw something that may have been a flagship initiative for their community that could perhaps help them make it to the big time in scientific research. And it was going to be stolen by these physicists, you know. It was -- and I remember statements or utterings from a very good friend, Jim Watson. We were referring to the fat, slobby cigar-smoking national laboratory scientists that were doing this. This was the sort of the nicest things he said about us at the time.

So it was understandably that it wasn't exactly welcome with open arms by the NIH.

How do they muscle their way in?

There were two major studies that made that change, which, quite frankly, from the very beginning, I thought was the right change, even though I'm on my community at the time. I wasn't exactly very popular.

There was the OTA study that was done. And then the national academy study by Bruce -- Bruce -- tell me the -- [laughs] --

Oh --

-- Albert -- Bruce Albert. You know, once those two studies came out, that, in some sense, validated their need and the timing for this particular project and, you know, in many respects endorsed it in whatever form it was presented at the time. Once that happened, it was much easier for the people within NIH to organize and --

Was there anybody sort of higher up in government in the White House or on the Hill that said, "Okay, you guys now have to go work together"?

Well, I think, certainly, Pete Domenici, even though it was a champion of DOE science, also understood about the NIH. And, in fact, he's been -- he was very helpful to the NIH for many years over the years.

I don't -- I wasn't, you know, I was in government at the time, but I was in the trenches. So I didn't really have much access or knowledge about things at the higher levels. I know within the Department of Energy was Al Trivelpiece, the director of the Office of Energy Research, now called the Office of Science, that -- who was the moving force, who was, in fact, in many ways also like me, seduced by this project. And he just -- he didn't do it just for his own aggrandisement, you know, to -- but I think he understood that this was something that's time has come and he very -- he was very adept in managing his own bureaucracy. And also the folks at OMB, Judy -- there was a budget examiner, long gone now because she was a chain smoker and died of lung cancer, in fact. Judy Bostock was her name. She was not very senior in OMB but she also was one of these very dynamic -- she had a vision and she understood that this was a project whose time has come. And she was also a champion of the DOE because her OMB responsibilities were there. So she was also another person that I know.

And I'm sure there's probably other people up the ladder in the White House who may have been seduced, but --

Should give Chris a chance to --

Yeah, well, I mean, I sort of have one question about Jim -- your impressions of Jim Watts's role during this early period that -- we'll go with that question. Then I'll sort of follow up on another question I have.

Go on, if you want to --

Oh, go ahead.

Sure. I mean, one of the things I'm really interested in is what as you consider to be the most pressing conceptual and technological challenges in the early history of the program, particularly sort of late ‘80s, early ‘90s, that had this be worked out before this was a really viable initiative.

From the technological point of view, I think sequencing was front and center. I mean, we -- the ways we did the sequencing were horrible. [laughs] It was more of an art than it was a science. It couldn't be scaled up very much. And as much as one said, "Well, you got $3 billion, you know, and you can still do a lot," there was -- there were some moments when we felt as if we had

launched something that was going to crash because we didn't have quite the technology for it. That's the way we felt. So that was the biggest challenge overall.

The second one was the communities, generally, were not into information technologies. There were only a few bioinformatics people, and, you know, there was very little understanding about what would have been required in terms of system approaches to what we were doing. This was an engineering project. And it wasn't quite the shot to the moon. It didn't require the kind of rocket science that was required. But it was along those lines. Yeah, I mean, there was a lot of biology associated with it and insight that needed to be had, but it was mostly technology. You know, we had to do it on scale, and you had to do it accurately and you do it fast and efficient. And quite frankly, I think that was one of the nightmares we had through almost the entire early part of the project. I can't put an exact date, whether it was '97 or '98 and so on, but many of us -- or some of us at least, around those times, were having nightmares about this was going to crash, and it would be one of the most embarrassing things, you know, we ever were [laughs] involved with. So…

What saved you?

Ari Patrinos:
You know, there I'm going to be a bit parochial. I think the fact that the Human Genome Project still had many people that were converts from the physical sciences that had a more can-do attitude. They were more familiar with large projects, and big systems, and many big teams, and so on that that wasn't entirely unfamiliar turf. So, mean even that was one of my -- I mean, I had already gone through the management of a fairly big program in global climate research, which involved scientists from many, many disciplines, from many agencies, from many universities and labs. And it required, you know, getting together and agreeing with some things and trying different things, but doing it according to a system, not as a result of knee-jerk reactions or, you know, religious beliefs, and, you know, the ineptibility [spelled phonetically] of some outcome or so on. It was more can-do business engineering type things.

Is it a cultural difference, though? I mean, you know, we know that, you know, the Manhattan Project brought on all these people to the desert, to Los Alamos and Alamogordo and all that part of the world, and they figured out how to work together to solve these by hand -- these calculations -- to figure out the physics of, you know, of fusion -- or fission, I guess, is the first round. And, you know, there was this culture of, you know, multidisciplinaries working together on a common project and solving problems together, which was very different than the sort of fractious loner biological community.

So was the -- can you just talk about that cultural difference and how critical that was, because genomics, as a field, is quite now different than the rest of the R01 research at NIH.

Yeah, mine is still very much a minority in the pursuit of -- and I'm not putting down R01 grants. In fact, that's the --

No, no, no, but talk about that culture difference and why that difference -- if that difference was important to the success.

I think it was. You know, it was very important to the success. I don't know whether either one of those two areas of research are more -- I mean, maybe it is. Maybe in the physics world, beyond a certain point, you can't accomplish very much on your own. You can't accomplish very much with just a small team. You know, you have to scale it up considerably in terms of the machines that you put together -- again, like surrin [spelled phonetically], for example. And this is not something -- in order to find the top quark, for example, you know, this was not going to happen with a few very smart scientists on a -- standing in front of a blackboard. I mean, it required the hardware to do it. And that costs a lot of money and needs a lot of people, needs a lot of different skills. It needs the ability to work together across different skills, work together even though you don't understand each other's science. But there are some places where they overlap and interface, and those are the ones that you sort of -- and you also have to dig big science. I mean, you have to get turned on by having a big community that sort of strives for the same objective. Even though, as Rutherford said, you know, it's very nice to have big teams and so on, but I put my trust in that misanthrope scientist underneath a staircase, you know, that's sort of wanting to go at it alone. They're still going to be the ones who will make the major breakthroughs. But science today probably needs the teams more than it needed it before.

Can I ask one other sort of big picture question? Could you -- you sort of talked about it a little bit, but talk -- just give me a contrast between sort of science of discovery versus the hypothesis-driven science and how that conceptual struggle played out, especially in the early days of the Genome Project.

Well, I was always been -- and I'm always a very big fan of Freeman Dyson [spelled phonetically]. So he's one of my old-time heroes. And he captures this in imagined worlds, one of the books he reads. I mean, he describes it, and what he said. He said, "There are two kinds of scientific revolutions. There's a concept-driven scientific revolution and a tools-driven scientific revolution." In the former, you have to explain all things in new ways. In the latter, you discover new things that need to be, you know, explained. And guess what? Guess what's more exciting and ultimately more impactful? Not that the former isn't important. But the impact is in the latter. And it's what happens when you turn the telescope to the heavens and you find stuff. You don't look -- you don't know what you're looking for, but you find stuff. Astronomy was that way in some -- and I think in some respects, the human genome was that way.

Now the discovery science is sometimes, and to a large extent, not something very popular with life scientists. You know, you -- and in many ways, it's not to take away from the hypothesis-driven. Hypothesis-driven is much more orderly. Pose a hypothesis, you describe an experiment, you conduct the experiment, you either confirm or refute. And regardless, you have the next step. If you refute, another experiment. If you confirm, then you make the next step ahead. And that's how science advances on all fronts.

Well, that's why the genome was, in many ways, alien for a lot of the life scientists, and as you recall, they said, "Well, we're going to spend all this money for just 2 percent of the genome that's only important, and the rest is junk?" You remember that. I mean, that's -- it was just this notion of, if you acquire a whole bunch of data, and it's in a field that's new and so on, shit happens, you know. [laughs]

That would definitely be the technical term. And Jim Watson, one could argue, is the ultimate hypothesis-driven kind of scientist. I mean, when he went to Cambridge, he knew that DNA was important, and he wanted to discover something important about like its shape and how it works. And so he focused on that question. So -- but he became, then, later the leader of the Genome Project, at least in its conception and its politics. So how -- so talk about Jim Watson, his vision, and, you know, given his history, how that changed to become a supporter of this big science enterprise.

Well, of course, you know, I didn't have very many interactions. I had met him a few times and so on. Some of it -- some of his enthusiasm about the project was, in many respects, the fear that that would be taken away from his community and it would be run by these terrible people in the DOE labs, for example, that he never had much empathy for. And from his point of view, perhaps I can understand that. And so some of it may have been simply just basic human primatology. You know, this is my turf and somebody's trying to take it away from me and so on.

But, at the same time, he's a very smart man. There's no question about it. And he realized that as this project was better and more and more articulated, that, hey, these are opportunities here that maybe even I didn't think about those. And getting the imprimatur of OTA and especially the academies imprimatur with Bruce Albert's committee made a big difference.

[unintelligible] made a huge difference in the politics of it all and getting the financial support --

Yeah, and he -- I mean, he was masterful, and we give him tremendous credit for the fact that he started the ELSI program, and the ethical, legal, and social implications of -- insisted very early on that we need to focus a chunk of that dough that we were getting to doing some of that scholarly research and outreach and education. So --

When the physicists at DOE heard that, what could possibly have been their reaction?

I think we got dragged into it kicking and screaming. In retrospect, we were very happy that we were dragged into it kicking and screaming. It was a very smart thing to do. And I think it's particularly important for a discovery-driven enterprise like the Human Genome Project, where you go out fishing for stuff and, you know, you need to have a -- your compass. You know, you get your ethical compass in place, because, as I will talk this afternoon to the meeting here, you know, you may get something called apophenia. Apophenia is when you see patterns in

nonsensical data, which is, in fact, the human trait. It's the way our brain is wired where we like to find things that aren't there. You know, whether you find a, you know, the image of the Madonna on a ham-and-cheese sandwich, or when you take a shower and you listen and you think you hear a radio playing. It's Bing Crosby singing or something. That's very natural in humans. You know, our brains are wired to try to see patterns where there are none.

So when you do discovery science, you may have a tendency to find things or see things that aren't there, as opposed to when you have a hypothesis, you know exactly what you're looking for, so it's either yes, or no, or maybe, or so on. But when it's wide open, you know, it's -- lot of people looking at the face on the moon, you know, all these things that you've seen in the past. And so you got to have that kind of compass so you don't veer dangerously into that space.

Yeah, one of things, I mean, that you bring up about patterns, which leads me to my next question, which is since genomics was -- and the Human Genome Project was already considered to be sort of a data-rich science, which is a really new problem because biology is a data-poor science in many ways, when did data sharing first become an issue?

Well, with respect to the data sharing issue, I have to give tremendous credit to Francis Collins, because he saw very early on the importance of data sharing, and how it could become both a facilitator but also a huge obstacle in progress. And so he was very much behind some of the somewhat aggressive ways by which we wanted to share information even when it didn't make any sense practically, but at least symbolically it was very important. Again, for the reasons I was describing earlier with respect to technology, we knew that this particular enterprise -- the actual sequencing of the genome itself -- would not have taken place in one or even two laboratories. I think politically it was obvious that it was going to be shared across many centers.

The number is, you know, something that I think personally it was probably too many centers, from the point of view that -- being a business. But it wasn't a business. It had applications and relevance beyond just the actual task itself. So I won't say anything beyond. But there was clearly too many centers, and therefore there would be a lot of overlap, and you had to make sure the standards, the quality standards, were universal, as common as possible, and you wouldn't be able to do that unless you were set up -- set up mechanisms to have the data sharing be effective, fast, reliable, and something that the physicists had already experienced in some of their big machine and collision things that was done. So, in some way, we borrowed and stole from that technology and that experience opened --

Just going back to human behavior, or, you know, [unintelligible] the biological community wasn't always so forthcoming, was it?

Not at all. I mean, nobody ever wants to share their data. I mean, let's face it, it's a natural researcher's trait that they want to at least hold onto it until they can squeeze whatever they can in terms of publication and recognition. So, nobody's naturally forthcoming with their data. So it had to be dictated. It had to be made, you know, a condition of one's involvement. And there, as I said, I give tremendous credit to Francis, who put both muscle, you know, strong-arm and

sweet talk people into going along. It was masterful in that respect. I didn't have any problems with our people because most of these people were conditioned to the sharing and the exchange.

Do you want to ask another question, Chris, or would you like me to?

No, you can --

So actually one of the things that -- so going back to the early days and one of the things that I've always been interested in is the development of the strategy of how to go forward. So technology was clearly one of the issues. We weren't going to be able to do slab gels and do three billion base pairs. But the genome's a big place. It's split over all these chromosomes. How the heck you find your way around? The decision was made to do this mapping stuff first and then do this back-by-back kind of sequencing. How did that evolve and how much controversy was there around that? Because I recall that there was a proposal long before Venter came along -- Dr. Venter came along -- about doing shotgun sequencing and, you know, Green said -- Bob -- Robert Green said that's never going to work. So talk a little bit about that to date, and how we got to the strategy that went forward, if you recall --

Phil Green, you mean.

Phil Green, I mean. I'm sorry. Yes, you're right. My mistake.

Okay, another sort of controversial thing. When the Genome Project was launched and money started flowing, you know, centers were created, and little empires were built, including three at our three national labs: Berkeley, Los Alamos, and Livermore. Some good work was done, but, quite frankly, the focus was not on the job that we had promised, which was to sequence the damn thing, right? People started putting ornaments in this Christmas tree, you know. They wanted to do other research. I mean, yeah. So the objective was always there but the understanding was that this was a 15-year project. Money was going to be growing as it continued to grow. So what's the hurry? Okay? What's the hurry?

Yeah, we're going to do some mapping, and we're going to invest in some of the technologies, and I think eventually somehow it's going to happen. And I think both the scientists -- the key scientists, not just within our community in DOE, but also in NIH, and even some of the program managers, perhaps, either because they were so totally immersed and so totally, you know, jazzed up about this project that the ultimate and perhaps the most important objective was too far in the future. And you could always argue that, well, the technology isn't quite there, so we're not going to take on this big thing. Let's do a little bit more of this and a little bit more of that, and this whole notion of mapping, and we'd do them -- it made sense, you know. If you want to discover, you land on an island, never done before, and you want to, in a sense, explore it, you got to do the mapping first and find the milestones and whatever the, you know, the forest is.

And then slowly, as you do the mapping, you can then get into the details of that. So that was the -- and I think -- we were heading towards a disaster that way.

Really?

Yeah, we were. I mean, I think what Craig Venter did for us was a swift kick in the pants that sort of sobered us up and said, "Oh, shit," you know. [laughs] We are -- this guy is going to beat us, you know, to it, and we going to lose all this. You know, and all this was a lot. You know, it was little empires built and communities and cultures, and, you know, scientists don't care much about money. So money, at least on the public side, was never a big thing. But it was prominence, and glory, and publications, and, you know, workshops and…

So talk about Craig drops into the middle of this stuff that's been going on for five, seven years in the mid-1990s. And he starts working here at the NIH and doing his own thing. But then he really -- but then he gets lured away with private money, and things start to get -- start to snowball. So just tell us your perspective of his arrival on the scene and the impact of it happening.

Well, I was lucky, of course, because I got to know him reasonably soon, and we hit it off very well, you know. And, in fact, when he sent me a proposal about shotgun sequencing -- that was in '95 -- it was -- I was in the job just for a couple of years, in '94 or '95. So he sent me the proposal for haemophilus, you know, the -- and, know, I'm no expert, but I really got interested in this, asked a few people, cautiously, because, you know -- and of course, the response I got, "Well, they probably won't work, but, you know, it's kind of interesting. Probably worth doing." So I tried to fund it. But it took longer.

I had proposals in, and I wanted the reviews. And, in fact, I overruled. That's one of the benefits of being in DOE. They give you enough rope to hang yourself. So it's not like NIH, where you just fund what the study section tells you. You can go against the reviews when you're in DOE. You can't do it all the time, and if you do it consistently, you know, they finally get you. As I said, they give you enough rope to hang yourself.

But this was one of those cases that I overruled the reviewers. But I didn't get it in time, and he had already gotten some private money and did haemophilus. But I was right behind there with mycoplasma genitalium and pneumococcus genoccia [spelled phonetically]. So I was convinced that that had potential. And when I brought it up to some of our advisors, you know, they said, "Well, Ari, this is a microbe. It's just only got a million base pairs long. You can't do the same thing with humans." And I said, "Why not?" "Well, it's a complicated." "Why is it complicated?" "Well, you know, it's 3 billion, and you need a big computer." Ha! Big computer? I mean, computing is growing by leaps and bounds. At the time, when I was in DOE, the people in the supercomputing divisions were begging me: "Get me some biologists." You know, bribe them. I was bribing our biologists: "Please come up with a problem, even if it's trivial, where you need a big computer because I want you guys to start standing in line to get lots of cycles for what you need."

So that argument didn't wash with me. You know, we need big computers, and -- so when Craig, you know, made that -- I knew about it way, way before, of course, it was announced. And I was sworn to secrecy, which I kept, just as I did with Francis and -- and in fact, at that time, when he was presenting it to me, you know, apart from the just -- some of the bombastic statements and so on, I thought it would be one way but which we get that swift kick in the pants. I was not getting much traction from our genome centers. I mean, not -- I mean, any science manager, research manager, however power he may have or she may have, you can't do everything. I mean, we did have quite a bit of control and power, you know, over the labs and so on. But it was very frustrating, try to convince these people that you had to put aside some of your very interesting ideas to do research and focus on this job at hand. And all of these people were saying, "Well, this is just an engineering job. I mean, where's the results? Where are the payoffs scientifically for me? Where am I going to get my publications if I devote all this money and all this energy into just doing this routine sequencing?"

So, I mean, I also got together with Marv, who was a very -- worked for me and was a -- but a very good advisor and very, very thoughtful. And we said, well, why don't we encourage this because it can force us to then heavily weigh on in the labs to get on the job.

Encourage this -- the competition from Venter?

Yeah, yeah.

And so are you saying that your own labs were like, "Eh." They just weren't producing stuff. They weren't really doing sequencing. They weren't -- some of them were --

I mean, they were doing minimal sequencing. And most of it is poor quality. And most of the energy was going into research. Some of it, I'm saying, is pretty good. A lot of it was genetics research. They all came from the genetics world, pretty much. They were leading this effort. They had not appetite for an engineering undertaking and -- first of all, you know, they were competing among themselves. Even though they all got the same amount of money, I remember when I took over the job, it was 10 million each for the three centers. And I said, "Well, how come it's 3 million?" I said, "How come it's 10 million?" I mean -- they said, "Well, you know, it's 30 million that we have for the centers, so it divided by three." And I go, "What? That doesn't make any sense." You know, we got to put some competition.

Well, that sort of rang alarm bells among the labs. Some of them thought, "Well, it's a good idea because I think we're better than the others" -- Berkeley people, for example. Others said, "No way." I mean, this is something that -- you know, this is really stepping on our turf. So it was frustrating in that respect.

So, bless his heart, Craig came in at the right time. We thought we'll ride that opportunity to make the changes we need to make.

So you brought the creative tension. Or at least you leveraged the creative tension.

I leveraged the creative tension. You know, of course, you know, I was hoping that Craig would be more diplomatic, but, you know, everybody has the defect of their qualities. And so I wasn't -- I guess I sort of knew that it was not necessarily going to be a very welcome thing with Francis, and -- but I still thought that on balance it would be helpful. And I think maybe a few years from now -- Francis probably won't comment on it -- but a few years from now, he may actually agree and say that, in many respects, I was also helpful to him in terms of kicking the butts of his genome scientists who may have been disinclined to do serious sequencing.

Despite your belief and trust in big computers, do you think, in your heart of hearts, that the 3 million base pairs of the human genome could have been assembled by software alone, without the scaffolding that was provided by the -- by back sequencing to order the data?

Yeah, I think I do.

Really? Why?

I think I do.

Why?

Because I think in the process of trying to do that simply with the software, the -- you would have probably come up with ideas. Now, there could have been some interventions that you would have to do or some additional research here and there. But I guess I always believe that you learn by doing. I mean, undertake something like this, even if you fail first and fail again, I mean, you'll learn stuff that will help you adjust and make the -- so, we can't prove this. We have to go to a parallel universe and see whether it can happen. But that was my belief.

That was one of the more interesting debates that came out of this, I thought.

And I think it never got settled because I think it's still raw nerves. But I think historically, you know, 10, 20 years from now when some of that passion is abated, we may settle this. We may be able to settle it.

It's -- I mean, it's interesting. And I don't want to go down this rabbit hole too far. Do you know this guy, John Coddington down at the National Museum of Natural History, is doing this project where he's trying to sequence basically the world. He had this enormous collection of all these

specimens from across the planet and evolutionary time. And when he gets FARO from mammals, he can't put anything together even now. So they'll do shotgun sequencing and the algorithms that they have for assembly just aren't working because they don't have a reference to go back to.

I see.

So it's -- and that's sort of contemporarily why I was -- I still think that this is kind of an interesting question.

And it needs to be answered.

Yeah, yeah. And I know that when Waterston, Lander, et al. wrote their paper answering that question, they had point of view.

Of course they did. They're wonderful people.

They are. And -- anyway.

Well, I'm really just sort of fascinated by your conversation because if you talk to a lot of historians to do the history of the Human Genome Project, they consider one of the big turning points to be the development of the complete map of the human genome in '95. But from what I'm hearing from you, that's less than -- that's less than --

They may be right. I mean, it's just my opinion. I don't -- we went down that path -- down a path. We don't know what would have happened had we followed another path. So -- but that's my conviction.

So before Dr. Venter came in, you would think that the picture you're presenting is that it's a field that's sort of somewhat overpopulated and a bit risk averse and very much sort of in their own cultures.

Yes.

That's a very interesting --

I mean, even in terms of the life scientists, the genomicists, they probably were a breed apart from their more conventional communities. But still, I mean, they still had elements of that

isolation, they had that -- and as I said, the same things with the DOE -- with the DOE labs. There wasn't a very strong incentive. I mean, let's face it. Nobody was after us in terms of, "Well, how much did you sequence, okay? And when are you going to finish?"

At that time, we were riding high. Everybody thought we were the cat's meow. You know, we were going to solve every problem that you ever had. So, you know, get off our backs, you know. We'll do it when we think it's the right time. And everybody would sort of reflect and praise us, and, you know, give us more money. Money kept going up. It was -- so --

So in those salad days, can you tell us a little bit about the background and the creation of JGI, about how the Joint Genome Institute --

Oh, yeah.

-- came about, and why it ended up where it ended up, and who the key players were and --

So shortly after I took over, which, you know, I was acting in '93. And I got the job, you know, in a non-active program.

The title of this job? What's the title?

Director for Biological and Environmental Research in the Office of Science. It was March of '95.

So the first thing I did -- because I had it planned all along. I didn't want to do it in an acting capacity because people would blow me away. But right after I got the job, you know, there were alarm bells that rang across the labs because they had a -- they got a hint about what it was all about.

So Marv and I took a trip right away, and we visited all three of the labs. And they were just panicking. And we went to all three of these labs and scrubbed them, and we came back and we basically said, "Oh, shit." You know, "This is not going to work." Entrenched communities, different cultures. In all -- in each one of the labs we heard how bad the other two were, how irrelevant their work was, how unwilling they were to help participate in some of their other activities. I mean, it was just like -- so we had to shake that place up. And, of course, we had to go get the support of our boss -- at the time, Martha Krebs -- who was a product of Berkeley. She had worked at Berkeley before she was picked by President Clinton to be the -- so we knew that this was a lab person. She had worked up on the science committee as well. And so she had a lot of loyalty to the labs. She thought that they were important and so on.

So before we did something that would embarrass her, and we went to her and we explained what we thought the problems were. And we asked for her support in terms of making big changes in the labs in order to meet the challenge that we felt was looming and was important for

us to do. And she gave us unconditional support. You know, she said, "If you guys think this is the right thing to do, I will support you because we need the labs to shine on this." This is not a case -- the labs were in trouble overall at the time. Hazel O'Leary was the secretary of energy. And she wanted to do a full-scale review of the labs and -- now people remember Clinton as being a big friend of science. But he wasn't a friend of science [laughs] until the last year of his administration. And he was talking about cutting back on a lot of things. And so people had forgotten this about Slick Willie. [laughs]

But you guys came to her with a solution. You had a solution --

Yeah, no, no, no. It was -- so we -- I got -- what I managed to do, which was, you know, a smart thing, in retrospect -- at the time, I didn't know -- I went to the deputy directors of the three labs: Pete Miller at Los Alamos, Jeff Wadsworth at Livermore, and Pier Oddone at Lawrence Berkeley National Lab. So they were in town for something, and I sort of hijacked them and took them out to dinner, and laid out my strategy and what was at stake and what I thought was very important. It's a -- and I got the same unconditional support from them as I got from Martha, which was, I think, especially Pier Oddone, who had the biggest center. They were aware about what the potential for this was. The funding, in terms of their empires, was trivial. It was the potential embarrassment that they wanted to avoid. And they were savvy enough to realize that their own people were, in a sense, just too narrow-minded, living in their own. And they'd rather have somebody from Washington come in and make those unpopular changes rather than them doing it, because the can always turn to their people and say, "Hey, I tried to defend you, but this jerk, you know, he's -- he doesn't want to change his mind." Not that they would ever do that, because all three are very good friends now, I mean, and we've had -- they're tough people and they didn't get those jobs for being -- you know, for not being tough in some of that.

So then the decision was to create one center, and, in a sense, do it freestanding so it doesn't identify with any one of the labs, insist that it be, in some way, collaborative, that scientists from all three labs participate in whatever their strength was, that we will institute, you know, serious reviews of everything that was done, and that the objective was to be part and parcel of the national program. There was not going to be an isolation. And one of the first things I did is got together with Francis. At the time, when he first met me, he couldn't figure me out, you know. He probably -- he was also relatively new at the time, so I don't think he trusted me or believed me that much that that's what I meant to do. And I said that we will sort of be part and parcel of the national program and the international program eventually. And there ain't going to be much isolation. You're going to be scrubbed the same way everybody else is in the overall community. And money is going to be handed out on the basis of need, then merit, and nothing else. You know, that was the…

I got the support of the regions, of the University of California. At the time, the University of California was, in essence, the manager of all three of those labs. Again, this is a bunch of highfalutin mostly physicists. You know, they like to come together and pontificate. They know about the research project, about the genome project. So they saw immediately the glory that they would also be associated with if they kind of made courageous decisions and so on. And that was very important because they supported me right away.

The person who was chairing it was the subsequent -- he was the last of the University of California at San Diego. The name will come with me -- to come to me.

San -- not -- Shinsheimer [spelled phonetically] was not --

University of California, San Diego. Anyway, he was -- so there were a bunch of physicists there who really got it and, in some way, weighed in and provided support, not that I didn't get the support I needed from the labs.

There was a lot of howling. There was a lot of complaints and so on. But we rode that storm and we insisted, and, you know, the first thing we did, we wanted a leader, and we didn't want to get any of the three leaders that were already in place: good scientists, good people. And we had already identified this odd guy bioinformaticist, but originally physicist, who, whenever we would have some of these early workshops, because there were a bunch of workshops and meetings that we had, emergency and otherwise. Elbert Branscomb. So I kind of liked that guy. You know, I didn't know him before and so on. He was a little odd, mischievous, and so on. And so we wanted -- and he was the deputy to the director at Livermore: Tony Carano [spelled phonetically], passed away now. Rest in peace.

So we sprung this on people and said, "You know, the director of the JGI will be this guy, Elbert Branscomb." And everybody said, "Albert, you know, he is just deputy to -- wow, he doesn't know" -- it turns out he was -- that was a very good choice. Albert understood, he was all for merit and for meritocracy and competition. I mean, he didn't have any delusions about NIH. I mean, he -- I think he was one of those cases where he gave a hard time to everybody, you know, his own people, us.

But Marv and I wrote him, and he, within a few months, sort of got into the job and delivered. And he understood what was important, a good a sense of humor. You've met Albert, right? I'm still in touch with him and --

And how would you assess -- what kind of grade would you give JGI's contribution to the overall enterprise?

I think we did our share [laughs], to be diplomatic. In many ways, more than just the quality of the product, you know, which we can argue and debate for a very long time. I mean, I'm -- bottom line, again, controversial statement. The quality of our overall product was pretty poor [laughs] -- of the old genome. I mean, if you look at it with today's standards, it's almost ludicrous. It's comical.

But -- now in terms of getting -- delivering the product and finishing the project, hey, you know, the -- and when these DOE lab people are led properly, when they're -- when it is explained to them what's at stake and what's the objective, they can do as well as anybody else. So I'm not going to give a grade, you know, with respect to what Lander did, or Waterston, or -- I think that's, you know -- but it's an interesting debate after a few drinks, to have that.

[laughter]

And so -- and what really scaled things up was, you know, Lee Hood's working it out capillary sequencing, stuff like that --

Electrophoresis.

So talk about that -- you said tools were really important in this. So Lee's down in -- Lee Hood is down at Cal Tech. He has this chalkboard meeting one day with his team. They map out these four machines. Tell me the story.

Yeah, Lee, of course -- Lee has been on our advisory committee and an integral part of our genome activities from the very beginning. He's an awful manager and [laughs] as I hope he'd also agree. So it's not like his managerial skills that were -- it was mostly his vision, and frankly, the insight that he had in terms of the capillary electrophoresis system. It's a -- you know, I think -- I think -- I can't say or prove it -- that a lot of this would have happened anyway, since money started flowing in the right directions in terms of technology development. And already there was a, you know, private sector sniffing around. This was an opportunity. It was going to happen. [laughs] Lee was also at the right place at the right time and invested in the right place with respect to research and so on. So these things almost have a spontaneous nature when it, you know, when the right opportunity comes up. It's --

It's just something in the air, sort of like Wallace and Darwin?

[laughs] Yeah, yeah.

But I wanted to actually just ask you a little more about sort of your role as an intermediary in all this -- in all these goings on. And also sort of you're in a very unique -- the program in biological and environmental research, it's a unique program within DOE. I mean, does that -- how did that facilitate things? As the science is moving forward, how did -- you know, some reflection on some of you going between communities and making sure everyone's talking and maybe some handholding and something like that.

So I had the best job in Washington. I continue to say that. Even though two of my successors have said they retired after two years because they said they couldn't understand how I ever did it for as long as I did. You know, it's a very demanding job because you are in the bosom of the physical sciences, but you do environmental and biological research that most of the political masters generally don't understand. So you compete with the big boys and girls in the physical sciences, and frequently you lose out because you're not one of them. And that's -- but that way you learn how to, in some way, wiggle through some of these challenges. You probably -- the

fact that you are continuously under attack. Every new administration that comes in says, "Why is DOE doing biology?" That's the first thing.

Presumably, NIH isn't behind that, but sometimes I wonder. There are probably some people at NIH that say, "This is an opportunity to get rid of these guys. You know, they're been a thorn on our side," which is human nature.

So anyway, by being in that frequently under the -- under attack, you develop certain instincts and you get some toughness, I guess, that helps you. And if you also work with many fields, because the program that I managed, you know, it had a huge component in global environmental change, had a structural biology component, had a nuclear medicine piece, had an environmental remediation effort, and then had the genomics, whether it was human or microbial.

So, you know, running through all these fields and just having all the weekly workshop, and getting into there and giving opening remarks, and talking about your importance, your attention, and your thinking about it, you know, it forces you to sort of take ideas from one place, apply them others where it makes sense, or try them out at least and see whether they fit or not, and…

So I was very lucky in that respect. That's why I said I had the best job in Washington. It was very stressful. You know, at the end, I knew that I had to go because it was taking too much out of me. But, at the same time, it was a wonderful ride and to be in touch with so many brilliant scientists in so many different fields. It's a once-in-a-lifetime opportunity. And to be associated with two of I think the most important research initiatives that we've had in this country for many years, and that's the U.S. Global Change Research Program and the Human Genome Project, so to have a chance to do both, I mean, it's just -- I mean, if I was independently wealthy, I wouldn't have taken a nickel out of Uncle Sam for this honor to do what I did. Anyway, so this gave me insights and certain, perhaps, skills that were honed on the various tasks that were useful in this particular case.

I need to say that in the early days of the Global Change Research Program -- it was not quite like the Human Genome Project, but it was very similar in terms of competing agencies. There were three agencies that launched this program -- I'll give you a short version of this -- NSF, NOAA, and NASA. So they got together and they said, "Well, let's launch this program. The time is right. Awareness about the greenhouse effect now is rising, especially in the political world," and so on. So it's an opportunity to launch this program, try to understand the workings of the Earth system in its magnificent complexity with respect to physical climate system, the chemistry, the biology. And this is an opportunity. And let's launch this as a truly interagency program so that we get the support from all other agencies. But, watch guys, you know, we are going to be the three big dogs and we're going to allow other agencies to go along, but, you know, they're going to have to be the second tier.

Well, you know, I didn't want to be in the second tier, so I challenged that prominence, and it became ugly, and, you know, to the point -- I was too young and stupid to know better in terms of -- and reckless, you know, and so, to non-concur with a program that had the support of 13 agencies, to stand in front of OMB and disclose what you thought was a, you know, a mistaken approach on the part of [unintelligible] -- it's a long history. I'll write that book someday. But it gave me, you know, it gave me some skills, again, that were useful in the subsequent activities.

And just to put an aside -- not to toot my horn -- but next month, the National Council for Science and the Environment, and it's in Washington, big meeting, is making a lifetime achievement award to the architects of the U.S. Global Change Program, which are the representatives of the four agencies at the time, including yours truly, and our budget examiner, who was also very prominent in making this happen. So --

Congratulations.

Thank you, yeah. This is something that would be nice to see my three colleagues who I fought with --

[laughter]

-- but became friend --

But became close to, yeah.

Oh, became friends in the end. In the end, we were, you know, very close, and so --

So let me ask you a relationship kind of a question. So you mentioned Francis Collins early on here, and the first time you met him and whether he trusted you or not, and all that kind of stuff. Tell me a little bit -- or tell us a little bit about, you know, your first impressions of Francis, meeting him, and how that relationship developed. And then at the back end of that, I want to ask about the pizza party because --

Sure.

-- I know the story. You've told a dozen times.

Sure, no, no, no.

We need to record it. So tell -- Francis Collins. You meet this tall, skinny guy with a soft southern, you know, Shenandoah accent, and you thought?

So, you know, of course, before I met him, you know, I would get a lot of the input from some of the people, especially from the DOE labs. And "Watch this guy. You know, he's a snake oil salesman," and so on. You know, well, the more I got to know Francis, the more I liked him, respected him. I mean, I'm -- genuinely -- I was genuinely, still am, fond of Francis. I mean, putting aside any of the work-related stuff, I mean, it's just -- I was -- I am honored to have known him, to have worked with him, to have been his friend. And, you know, the fact that he calls me his friend is something that I cherish immensely. He was my neighbor also for a bunch of years, and both he and Diane -- and then we got to know them and -- but Francis is a very,

very special human being. And I use that term for maybe a handful of people. Craig is probably another one. Not many more.

Francis is certainly a very special human being, incredibly talented, dedicated, genuine -- I mean, almost to the point where you say, "Where's the catch?" you know. "He must have something." [laughs] I haven't found it. I don't think there is. It's just genuine, wonderful human being.

So I was both extremely flattered to be a sort of at the same table with him. I was, you know, very, very, and genuinely, grateful for how he treated me as an equal in the lot of the interagency; could have easily -- especially during the Clinton years -- blown us away, because DOE was in the doghouse. You know, there were times when he could have very easily moved some levers, and, you know, he's also very politically adept. And we could have just disappeared. Instead, he didn't do that. I mean, he wanted genuinely to include us.

You know, at sometimes, he had to be political. Sometimes he had to make decisions that were not popular with us or didn't necessarily help us. But in terms of the overall objective, I can't fault him in anything.

Can't say the same thing about Varmus. I think he sometimes was a bit of a bully. Francis was not -- never -- certainly never with me, a bully. And he disagreed with some of the things I did. He tried to change some of the things I did. But never was bully. He was just -- I mean, I can't say enough wonderful things about --

Scientifically, how was Dr. Collins?

You know, to the extent that I can judge him, because he certainly is more experienced, knowledgeable in biology than I am, I've always been impressed by how well -- how much he knew, how much he learned quickly, how much he was willing to learn, how much he was willing to change his mind about things. So I can't say enough good things. So --

Quick aside: You mentioned Harold Varmus, who was then director of the National Institutes of Health. You had issues with Harold?

Yeah, well, we did. I mean, there were times when -- I'll give you one example. When we tried to do a deal with Celera, and at the time, it was not as behind the NIH's back. You know, when things were starting to get real ugly, we thought that maybe if we could engineer or work some sort of even just meaningless agreement with Celera -- and meaningless, I meant some sort of collaboration that didn't really mean very much, but at least on the surface, it made it look good.

Francis was willing to hear me out. You know, he wasn't happy because at that time, it already turned ugly. But, you know, he said, "Well, let me see what -- you give me something that you" -- we wrote an MOU that we would present. And he made changes, and he worked it, and well our good friend Michael Morgan found out about it. And, of course, the Brits were just rabid,

foaming at the mouth. And they would never do anything that would, you know, enable any kind of raproshma there.

So through their connection, that this was the highest levels politically. It got to Varmus and Varmus wanted to put the kibosh on this. So there was some sort of a meeting. This is fact, and I've got the details in my [laughs] -- in my log book. Some meeting that Albert, Marv, and I were going to be at, and Francis and some of the other genome center directors would be there. And somehow they arranged it that I was called to do something else. So I wasn't there. Marvin, Albert were there, but Varmus showed up, and when it came down on them really hard about this MOU, they didn't know what was -- hit them -- what hit them.

I remember getting home after my other meeting, which, I know I was puzzled about it because it didn't seem like it was a very important one. But, you know, they had insisted I needed to go to this meeting. And they call me on the phone, and they were hysterical. I mean, I don't mean it -- I mean it, really. They didn't make any sense. And, you know, I -- so I screamed on the phone that's just -- "Shut up, guys. Sit down and tell me." And what had happened was that, publicly, Varmus had just berated them about this terrible thing that DOE was doing. And, you know, I thought that was -- I have a lot of respect for his capabilities, Varmus, and, frankly, he also -- I mean, I had a -- when he was at Sloan-Kettering, I had a friend who passed away, but, and he needed some attention, and Varmus was very helpful. So this was the one instant, however -- the incident, however, that I mention his bullying. And sometimes maybe you need to bully for the final outcome. And from his perspective, probably it was the right thing to do. Francis would never have done that. So that's the difference that I would draw. So --

It's very interesting. And so you were in the background working at trying to have some raproshma between these now publicly competing public and private enterprises. And you -- there is this famous pizza meeting that you arranged between Francis and Craig to try to have at least a public raproshma and have some -- the deal.

How did that come about? Where did the instructions to you to -- that this -- you needed to do this or -- how did it all come about, and what was the outcome? So just tell us the whole anecdote.

Well, I know I've told this story before, and of course -- and I don't think it's changed. It's not that I've learned any more. I've gone through my notes occasionally, because among my notes do I have a detailed report of all the three-way telephone conversations that Francis, Craig, and I had, to every minutia that they spoke of. And some of that needs to be shown some time, at least to the two of them. That would be amusing, at least, to some of them -- to both of them.

So, you know, I mentioned so many good things about Francis. And it was primarily because of how fond I am and was of him, how much I respected him, that I didn't want this whole thing -- of course, it was, you know, from my own selfish interest, I didn't want this whole genome project to end up in an embarrassment. You remember those days? It was getting very ugly. And the media was having a field day, just getting under the skin, especially of Craig, and getting him to say things that he probably -- he definitely should not have said and probably

wouldn't have said if -- so we were approaching a point of where it was like mud wrestling fight. And it was ugly. It was ugly.

And -- but I have to say, I wasn't worried very much about Craig. I realized that even though he has also a very thin skin, you know, and even though he will never admit it, he's a survivor, you know it. However that worked out, he's a smart guy. You know, his ideas are 100 a minute, you know. And he would flourish and he would get over it and go.

But I didn't know about Francis. I mean, I was -- I did not want this wonderful friend to be embarrassed, not to get, you know, not to succeed in what he had undertaken. And I think, in many respects, if this had turned ugly, I could have gone back to climate change. Craig would have started something else and done -- but Francis would have, you know, would have lost. He would have been essentially the biggest victim of a failed project. And I didn't want to see that happen.

So was it selfish of me to see this happening because I was -- of course. But I think a large part of it was my fondness for Francis and my ever-increasing respect, admiration, you know. I -- and I also think that generally in his interactions with Venter at that time -- mostly acrimonious and so on -- he was being a gentleman. I mean, he was being as forthright -- and Craig is Craig. You can't help it.

So, I mean, I had this unique position where I was friends with both people, with both of them. I -- they told me a lot of things in confidence that I didn't share with the other person. And I never felt bad about this, and neither one of them have ever said, "Oh, my gosh, you know, you should have told me this." Neither one of them has said that.

So I never got any instructions from DOE, like people have said and have tried to take some of that credit. No, I mean, I would be interacting with -- at that time, Martha had already left when this was happening. There was an acting person who was a really good friend. And I went to him and said, "You know, by the way, Jim, you know, I'm going to be doing some of these." Behind the scene, he said, "Well, you know, I trust you, Ari. You know, whatever you need, you let me know and I'll provide whatever support you need."

So Ernie Moniz was undersecretary of energy at the time. At some point, but well after this had -- became public, and we were at the tail end, I had gone to him and say, "Ernie, you know, you should know that this and this is happening." And Ernie said, "Ari, you know, you didn't -- this is a terrific. Just let me know what I need to do to help out." And so -- and that was the extent of the -- but otherwise, you know, there were already these failed attempts at raproshma by people that didn't quite do it the right way.

And I thought -- I also believe, still very much, that both Francis and Craig were, in a sense, victims of their own environments. I mean, they were enveloped in this cocoon of people who presumably, and probably correctly, wanted their better interest, wanted to protect them, and wanted to help them. But all of these people also had their own interests, you know. So I have the feeling, you know, maybe -- even including you, I don't know. I mean, I'm just saying this was my perception that the advisors, the people surrounding Francis and the people surrounding Craig -- and I know that for sure on the part of Craig -- didn't want any raproshma. I think there were this conviction that somehow we have to take this to the end, and there's going to be one

man standing; that there was not going to be any compromise. It's out of the question. And either -- both sides felt that it was a done deal. And in some ways, understandably so, you know, on the public. On the public, you don't screw with the U.S. government. I mean, let's face it. If you're going to embarrass the U.S. government, you're taking on a big risk. I mean, that would have not happened.

On the other hand, if you still squash the Celera thing and so on, and you manage to do it and you only end up with one program, Craig would have been a hero. I mean, he would have been more famous than he is now because he was -- he took on the U.S. government and he lost. And all these things are not as perfect as they would have been had he survived. I think he would have done much, much better had he been squashed, frankly. That's my -- he doesn't like to hear that, but it's true.

So I don't think there was much support within the palace guards of those two individuals for any kind of serious raproshma. So the only way to try to do something is to do it completely informally. And I had the right place since I was a neighbor of Francis. I would get together with Craig on Sundays. We would walk his dogs in the park, and we would sort of exchange news, confidentially or otherwise. And that's when I, you know, I kept telling Francis, "Let me try to do this." And he kept saying, "Well, I can't let you do this. I have to get buy-in from my center directors." I said, "Forget it. If you're trying to do that, it's never going to happen." Forget buy-in from Ruth, who was the director at the time. You know, and I said, "Francis, you're going to" -- this is one case where I pushed him.

And on the other hand, I went to Craig and I said, "Want would you think?" You know, "Let's have an off-the-record conversation." And I think he was already starting to worry. He told Heather -- at the time was his wife -- and his people there. And they all said, "No, no, no. You don't want to do that. Let's just whip their ass," you know. But Craig -- bless his heart -- I mean, he can be bombastic, flamboyant, you know, short-tempered, but he's smart. You know, I think he saw that this was probably for his own interest, better. You know, that -- so, you know, he said, "Let's try it."

And finally, at some point, after continuous -- I mean, at that time, I was meeting with Francis for breakfast, if you recall, almost every week or every other week. Finally said, "Well, let's try it."

So we got that first meeting. I asked my wife to take the little -- the girls were little at the time -- and take them out to the mall for a couple of hours. And it was not at the basement, that first meeting, contrary to this. It was in our living room. We got pizza and some beer. You know, it was very awkward and nervous in the beginning, but --

Who was in the room?

Just the three of us. Just the three of us.

And so how did that evolve, and how did that evolve to lead to the June 26, 2000 meeting at the White House?

Well, it didn't take long, even in that meeting, for them to loosen up. And beer helps, of course.

Absolutely.

And it was also very clear from the conversation that they were both feeling as if they'd been beat upon. I mean, it may be, to some extent, although neither one of them ever admitted or said anything to that effect, that maybe they didn't -- they weren't exactly better or best served by their immediate advisors, you know, that this was a case where they needed to show some leadership. And then, you know, just the fact that they felt that the media had not treated them fairly. You know, that -- they both felt the media was not treating either one of them fairly. Now they probably felt that the other person was treated much better.

So I think this notion of feeling a bit as victims helped a little bit in terms of bonding them. And, you know, I also -- another very important aspect that's not often mentioned in these descriptions of that time was that they're both scientists. [laughs] Yeah, they were ambitious. They're ambitious people and have other goals beyond, but science is very much at the heart of what they care for and hope for.

So once you get them going on some conversations about science, immediately the bonding is very powerful. And so it's just the fact that these two people -- and I was -- I mean, I would sort of help the conversation, and cut up the pizza, and we get the beer, and say a few things here and there. But it didn't take very long, and it didn't take very much for me to get them talking.

And at the end, I said, "Well, you know, yeah, let's have another meeting. Looks like this may lead to something." And both said yes.

How many were there? How many meetings like this were there?

Four.

Four.

Well, you were in one of them.

I don't think so, no, I was --

Oh, no. Yeah, you were -- well, there was the last one where -- boy, am I blanking -- Kathy [spelled phonetically] Hudson.

[affirmative]

Kathy Hudson, and there was a PR person so there.

Kathy Arboro [spelled phonetically] was the PR person that -- at Genome then.

I don't -- I have all the notes. [laughs]

Yeah, you have notes. [laughs]

I have all the notes. You know, the last one was -- I mean, it was all obvious. But the first three were still reasonably confidential. The second one was, in fact, in the basement where -- and by then, by the second meeting, we were already talking about what we could do. So it was almost like a given that we had enough common ground that we had to make this happen with respect to the raproshma. And it was a question whether we make it one, you know, whether we -- the program becomes one program, and some of the scenarios were unrealistic, you know. But --

Where did the idea for a tie come from?

I think it may have been -- that may have been one of my contributions because, you know, it made sense. I mean, why have a winner? You know, this is not all this business about, you know, this is not a race. It's about the human race, all these things that we said, you know, the highfalutin stuff that we said at the big event. And I think at that time maybe both sides felt I was reasonable because the risk of alternatives was unwelcome.

I think probably Craig -- both of them had a hard time selling it to their -- but probably Craig had a harder time than Francis.

Really? Why's that?

Because, you know, the Celera people were very arrogant and very sure of themselves. And they felt they had the wind in their back, you know. And let's say -- let's face it, the media and the popular news was on their behalf. It was David versus Goliath and those kinds of things. So -- and -- I didn't think they'd -- none of them -- and they're great scientists also -- had any clue about politics. I mean, bless his heart. Ham Smith was totally clueless.

All the other people in this -- I mean, the only savvy person there was Heather, who was negative to this because she felt that Craig had the upper hand. We've had a couple of conversations with Heather since -- well, it's sort of water over the dam.

So how did you feel when you go to that June 26, 2000 event at the White House?

Oh, it was wonderful. I wore this suit, by the way.

[laughs] And it still fits you well.

Still fits me well. Yeah, I -- in fact, I just noticed it when I was about to leave, and I said, "Oh, my gosh. I didn't wear -- I'm not wearing a tie." It wasn't -- but, yeah, it was a great day. It was a great day. It was tiring. We were all exhausted. And by then, of course, you know, the people in DOE had found out about it, and so I had briefed Ernie. But Ernie was sort of my shield. And Bill Richardson who was -- discovered the Human Genome Project, bless his heart, another bigger-than-life character. So, you know, it was very busy. And of course it came to the wire because there were still issues that had to be settled even hours before the actual event, you know, what Tony Blair was going to say. And, quite frankly, the Welcome Trust people were not particularly helpful. I think they were unhappy with this outcome. They felt as if it was -- they weren't consulted sufficiently. They felt they were partners with us and sort of betrayed them. So they had to do an about-face, you know, within -- so any -- I think there were probably trying to sabotage it even up to the last moment.

This was Sulston?

Yeah, Sulston, of course. And, you know, these -- a lot of it is sort of their socialist attitudes about, you know, being down on the private sector, which I found comical. I mean, it's a private sector that's going to give you the ultimate discovery. It was a great -- I mean, it was a great event. And we're still remembering, and it wasn't -- it wasn't -- I mean, it was a pivotal date, but we still had three more years [laughs] of hard work that needed to get done.

But Craig didn't really survive that next phase. What happened?

Craig was never very much popular with the management of, you know, senior -- the -- what's it, Tony White? You remember Tony White? He hated Craig. You know, he -- because, first of all, he thought that Tony White should have gotten the attention and the prominence that Craig did, which was absolutely ridiculous. And, of course, Craig had overruled them, or he had gone around them many times in decisions about Celera, frankly, correctly. You know, so he wasn't going to be there very long. And then Tony White got rid of him eventually, so…

Interesting. It's 11:51. I don't know what your schedule is. What's -- tell me -- who's coming to get you next, or what are you doing there?

I have no idea, but --

What time is your talk?

I think it's 1:00 or so, so --

And we probably want to get you some lunch. You have a burning last question you'd like to --

I don't have lunch. I'm going to be with the students. We're going to have lunch. So I have some more time.

Okay.

Yeah, I think the -- one of the questions that I have is -- unless you want to answer some more biographical stuff, is -- how much time do you think we have?

We can be here for another 20 minutes.

Okay, sure.

Whatever you're willing to do.

If they miss me, they'll come and get me.

Right, that's probably --

I mean, that's sort of the key. So in terms of, you know, just the crucial turning point, when, in your estimation, did you really think that this is a project that's going -- the Human Genome Project -- that's going absolutely be finished, and it's going to be an absolutely momentous scientific occasion. I mean, was that sort of after this whole Celera partnership was solidified, or was there some later date or earlier date where you came to that understanding?

I think it was around the time of the -- when it looked like it was going to happen, you know, after the second meeting especially, where I felt confident that it was going to be worked out.

If -- the competition between Francis and --

Yes.

But technologically, going back, you know, before that. I mean, when did it look --

Yeah, when did it look like --

When did it like look technically this was actually going to have to work. You know, we're mapping, mapping, mapping --

Right.

-- so sequence technology development is going on. When did it come to fruition that it looked like, "Oh, wait. Maybe we can actually do this."

That completion is possible.

I have these notes. But -- so it was probably in one of the meetings. I don't know whether it was a Bermuda meeting or a subsequent meeting of the center directors that we had. Some of those meetings, quite frankly, especially in the early stage, were excruciatingly painful, with the posturing by different individuals, you know, who had completely done an about-face in some of their beliefs. That's what -- sometimes I find it amazing. A lot of these people that are vetted as being the major -- and they had some incredibly narrow-minded views. I won't mention names, but [laughs]. So a lot of them in the early on was enough to get you very discouraged.

But I remember one -- and I have to get you the date -- one of the center director meetings where it looked like people were finally settling down to doing the job. I mean, there were -- we all sort of got a pretty good understanding about how variable the quality was going to be. You know, some of the centers were not as good as others in terms of the quality. And of course we had, for political reasons, brought in the G-19 or 20 or, Francis called it, you know, all these little -- or big countries where they had small centers, and they, for political purposes, and ones I endorse fully, had contributed pieces that, you know, would actually impact the quality overall.

But nevertheless, you felt that the five ones that are taking on the job were finally serious. It may have been partly the result of the, you know, the fear from Venter. Francis used that

effectively when he rallied the troops and basically said, "We need to scale up. We need more money, and we need to get more organized," and so on. He could have very easily continued the same pace, in which case I think Craig would have just embarrassed us. But Francis was very good in rallying. I mean, I think he probably surprised Craig by how effective -- sometimes good leaders are -- come out, you know, when there's a crisis, you know, like Grant. I read a lot about the Civil War. Ulysses S. Grant was that kind of person in terms of rising to the occasion when in crisis.

Do you think the development of the applied biosystems machine was a pivotal turning --

Oh, yes.

Was the ABI machine important? So why was that important?

Well, I think it, again, it was the standards of quality and the consistency of the quality with the machines, the service that was provided. [laughs] We used a lot of amateur machines in some way. And for us they did okay at the time. But overall, the ABI was the workhorse. And I think the company realized very quickly what was in store and what they could do. I mean, they made a mint. They made a lot of money out of that. But they moved very, very quickly and put in the right people within the company in place. I guess Hunkapiller was still involved there.

Mike.

Yeah. Mike.

He still around?

He's still around.

Oh, my God.

I did speak to him. I was trying to get him to speak to one of my colleagues who was investing in biotech and wanted input from -- and I felt Mike was the best person to do that.

So casting your mind forward -- if that's okay?

Yeah, no, that's fine. I'm going to follow up on your question probably.

No, go ahead.

No, I was just wondering, for example, how you came to lead the DOE and then go to synthetic genomics?

Well, as much as I love my agency, it's not as kind a place as the NIH, meaning that it's a very competitive place, and especially if you've been successful, the long knives come out after you. People have long memories and generally get even in some ways.

So I know that I was not going to be able to last very long, even if I wanted. But quite frankly, you know, I had been in the government for 17 years. I never thought I would ever last that long in there. But I only did it because I had these two great opportunities, mostly. Otherwise, I would have bailed out even sooner. So I was looking around. In fact, I could have even gone in another part of government. I had even talked to Francis about -- at some point I -- when it was bioengineering, institute was about to be created. I was sort of thought about that a little bit, but it never became -- it became an institute. And I was interested when it was a center because I don't have an MD, and therefore I wouldn't have been selected. But when it became an institute, it was obvious I wouldn't get it.

No one wanted to hire me to restructure their national labs. So I would have -- I could have easily gone in government, or I had the possibilities in the Middle East because I speak Arabic. So it was a big asset, and I like to do -- but then Craig totally ambushed me with this. You know, he had insisted in inviting me to one of his Hilton Head meetings. And he sat me next to a bunch of people who turns out to be the Board of Synthetic Genomics. And, you know, in the course of the conversation, he said, "Well, yeah, and I know who the president should be of this company of ours, and he's sitting to the left of Alfonso [spelled phonetically]." Said, "I'm sitting to the left." [laughs]

So I said, "Craig, stop right there before you say any more. I need to go back to DOE and tell them," because you know how DOE is ruthless in that respect. So -- but I was still stunned. And but then it was a no-brainer. It was something to start. I mean, I loved synthetic biology. You know, I did -- I don't know whether you know, but I funded some of the very early work against advice of the reviewers at the time. So, you know, this whole notion of the minimal genome that's still a bridge too far, but it was one of those things I pushed back in the mid-'90s as important.

I thought of it mostly because I felt that if you get the minimal genome to be really minimal, like really, really small, you could potentially get to the stage where you can numerically represent it in a molecule by molecule molecular dynamics system. You know, it's still a -- you know, the holy grail of a lot it.

But, you know, if it's really small, you can get much more computationally precise in doing this. So it would have been a challenge for people, you know, pushing the bleeding edge of computing, and, you know, something we're still doing. I've been involved in the planning stages of the exaflop computer. It's 10^{18} operations a second. So once you get to those kinds of speeds and sizes and so on, you may be able to do a lot more with respect to computationally modeling a cell, you know, if it's a minimal cell, so --

Excuse me.

Yes, ma'am.

Ari was supposed to be over in Natcher at 11:45.

Oh.

Okay, thank you very much.

We'll be there --

In a minute.

Ten minutes.

We're going to do -- yeah, just a few more minutes. And actually, if you want, I can drive you over there so you don't have to huff it, because I have to move my car anyway. I parked illegally because I was running late.

But I'm just curious, just sort of -- you -- so you have this sweep of history and all of this. Just cast your mind forward, and -- from today, and where -- how is genomics going to change the way we ask questions, the way we conduct scientific research, the way we end up treating disease? What's your forecast?

Well, I now believe that it's probably going to take a bit longer than we had hoped in terms of some of the impacts on medicine. Just things take time. It's a -- and sometimes you have to change cultures of people, and then that's difficult to do. So, some of our early hopes that we would get things very quickly probably won't happen. But they're in the pipeline. I'm convinced they're in the pipeline, as sequencing gets cheaper and cheaper, as more and more genome -- I mean, this is one case -- I'm a big Rolling Stones fan -- where time is really on our side. And it's not just increased knowledge, but it's just the additive nature of the knowledge, you know, the more information.

And let's face it. As you sequence more and more human genomes, too many things are going to pop out that are going to be obvious.

Male Speaker:
Truly unexpected things have been discovered.

Oh, of course, and more so. And of course, the -- you know, the exciting part is the fact that life

sciences has been -- has transformed. I mean, it's still very much a hypothesis-driven, and we want that to continue and support it. But at the same time, it's open to discovery-type research. I don't know, it's so reassuring now and pleasant to see the many disciplines that are sort of getting enveloped by life sciences. So many people that want to do studies in the life sciences, even if they come from engineering, from chemistry. I mean, a lot of these lines are blurred now. People don't ask you anymore about if you're in the field. I mean, it -- and then if you probe, you find out this guy has a degree in mathematics, you know, he was trained in being a chemist, an organic chemist or inorganic chemist, and has done these things.

So, I mean this -- it's changed science.

You observed that it's going to take us a little while yet to deliver on the promise of the Genome Project, at least in medicine. Was -- as is sometimes stated, genomics was hyped, was overhyped.

No, no, not at all, not at all. I really bristle at those kind of accusations. It was not hyped. And you -- you know, even the stuff that Francis gets criticized about -- I've gone through over some of his older statements and so on -- he was always very careful to say how much basic research still needed to be pursued. So, no, I think it was our detractors that -- accusing us of hype. And funny thing, we, in the program, didn't do enough hype. When you compare with the hype that the physicists do is they're sort of totally nonsensical -- well, not to them, of course. You know, I give them a hard time about all this billions that you've got and you still don't know what the universe is made of. I mean, you talk about dark matter, and there's like 85 percent of the universe and you don't even know what the heck that is? And you're criticizing us for overhyping? [laughs] No.

Fair enough. Well, we should be respectful. We should take you over.

All right.

Ari, this was a real treat. This was fabulous. Really, really fabulous.

It was my pleasure.

[end of transcript]