John Schiller, Ph.D.

April 28, 2023

Barr: Good morning. Today is April 28, 2023. My name is Gabrielle Barr, and I'm the Archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. John Schiller. Dr. Schiller is an NIH Distinguished Investigator, the Deputy Chief of the Laboratory of Cellular Oncology, and the Head of the Neoplastic Disease Section at the National Cancer Institute [NCI]. Dr. Schiller has received numerous awards, including the 2014 National Medal of Technology and Innovation, and the 2017 Lasker-DeBakey Clinical Medical Research Award, and was elected to the National Academy of Sciences in 2020. Today, Dr. Schiller will speak about the trajectory of his career at NIH. Thank you very much for being with me.

Schiller: It's my pleasure.

Barr: To begin, will you please share a little bit about your upbringing, including where you grew up, your family life, your early education, and any formative experiences that you feel have shaped you as an adult?

Schiller: That's a lot for the first question. I grew up in Madison, Wisconsin, in sort of the working-class side of town. I grew up in a family of five children. My dad was an Deere tractor and implement salesman and part owner, basically a small businessman. There wasn't a lot of precedent for academics in my family. All my grandparents were immigrants from Germany and not particularly well educated. But my parents really stressed the importance of education. It was sort of assumed that we would all go to college, even though my parents hadn't had a chance to do that because of their fairly modest upbringing in the 1930s and 1940s. The family always valued education, although nobody in the family except me really had a striking interest in science.

Barr: What made you interested in science as a child?

Schiller: I was always interested in natural phenomena—sort of natural history. I would memorize all the types of trees and identify all the birds and mammals and stuff in our area. I would read about them and how they made a living. It really started with an interest in natural history. I was never really interested in how my TV worked so I was never destined to be an engineer. It was just natural phenomena that I was interested in. That sort of led into my interest in science, especially biology.

Barr: You were more interested in nature than medicine? Did you have any inclination that you would go to the medical side of things?

Schiller: Well, it was interesting. Initially, during my undergraduate [studies], I was really what I would call a "knowledge purist." I thought you should study knowledge for its own sake, that it had intrinsic value to generate new knowledge, and that it was even somehow tainted if it had some sort of practical applicability. I was really looking to this ivory tower experience. It was only later that I really became fascinated with taking this basic knowledge and translating it into something that could actually help people. It was a gradual development in my career outlook. Right now, I'm totally fascinated with that concept of taking complex basic ideas and turning them into simple interventions that could help people.

Barr: Speaking of your undergraduate experience, will you talk about your time at the University of Wisconsin, where you concentrated on molecular biology? Did you have any mentors, courses, or lab experiences that

really made a deep impression on you or influenced the course of your career? Can you talk a little about the emphasis on translational science that you had at this point?

Schiller: I think I touched on that a little bit, at least the last point. I went to the University of Wisconsin for two reasons. One, it was really a premier university for biochemistry, genetics, biology, and the emerging field of molecular biology. I actually majored in molecular biology, and there weren't many schools around the country that had degrees in molecular biology. That's what I was interested in, learning about the basic features of life on a molecular level. The other reason I went there is, because I was a resident of Wisconsin, it was just so much cheaper than any other place I could go to. My parents were paying for college. I just couldn't think that it was worthwhile to go anyplace other than Madison. It's a lovely town. It's a great campus. I had a wonderful experience. I had a lot of friends there.

Barr: Did you live at home?

Schiller: No. It was really nice. My parents paid for me to live on campus for the first year, and then I had an apartment with friends after that. But really, the biggest influence on my career probably wasn't an individual, but a series of courses called Biocore, which is still running to this day but was just starting then. You study the breadth of biology, starting with molecular, and then cellular, and then organismal, and then population. They had lectures by premier people in the field. Especially on a molecular level, I was totally stunned with the idea of the unity of life. Even though I was studying all these different animals, I didn't realize that on a cellular or subcellular level, we all basically do the same thing. We take the same molecules and break them down into the same smaller molecules. We take the information from our DNA and generate proteins with it in basically the same way, whether you're a bacterium or a person. And this unity of life just blew me away. That was one of the things that really made me want to try to study this process and these common features among all organisms that are so fundamental to life.

Barr: What was it like being at the University of Wisconsin in the early 1970s? That was a very interesting time.

Schiller: It was interesting academically because molecular biology was just starting to explode.

Barr: But also, socially and politically in Madison.

Schiller: Socially and politically, it was amazing. The year before I started, actually, the campus didn't give any grades. It was shut down part of the time because of the Vietnam War. When you would go there, there would be marches coming through the dormitory areas, and they would try to recruit people. You had to make this decision which side you were going to be on because it was a very conscious decision—whether you were going to march against the Vietnam War, or you were not going to march against the Vietnam War. The interesting thing in my freshman year is that there was still the draft. I still remember this very clearly. The guys in my dorm would sit together to basically hear what their fate was going to be. If you got a low draft number, you were going to Vietnam—or to Canada. I distinctly remember, I got a high draft number, so I wasn't going to be drafted and go to Vietnam. I was so happy, but a couple minutes later my roommate got a low number. Immediately, of course, he was crestfallen, and immediately thinking about going to Canada—because if there's one guy who was never destined for the military, it was my roommate at the time, Billy Grogan. It turns out that they actually didn't take anybody in the draft. It was the first year that they didn't draft anybody, but we got all the numbers. You can imagine how this could really change your life—just sitting there wondering whether you're going to be able to continue staying in college or end up in Vietnam. It was a very troubling time. People had to make very important decisions in their lives that kids today don't even think about.

Barr: Not to foreshadow, but do you think that some of the issues discussed when you were in college have influenced your thinking in terms of making vaccines and therapeutics available to the public and disadvantaged countries and to have a more universalist mindset?

Schiller: I think maybe what it did is sort of made me question everything. It's like, if this is the dogma, don't necessarily believe it, because everything everybody's saying isn't necessarily right. To be sort of bucking trends quite a bit in my career, I sort of enjoy being in that space. I think part of that is from going through that era, where everything was being questioned—the basic way society was working back in the 1950s and early 1960s. People were questioning if that is the way we want to run our lives as we get older.

Barr: What encouraged you to attend University of Washington in Seattle for your Ph.D. in microbiology? How did you choose to focus on diphtheria for your dissertation?

Schiller: The reason I went to University of Washington was twofold. Actually, threefold. One, it was a really good school in microbiology. It was one of the top microbiology departments in the country. Two, it was on the West Coast. I had grown up in the Midwest, and I wanted to live on the west coast. I applied to just two schools, the University of Washington, and the University of San Francisco, because those are the two cities I wanted to live in. And three, as an undergraduate, I had worked as a counselor for four summers in a children's camp in the foothills of the Cascades, so I had a lot of really good friends from the Seattle area. I love the area. I always thought that it's a place I would want to settle eventually based upon that experience. It's natural to want to go there. When I came to Seattle to start my graduate school, I already had a cadre of friends and ended up living with them in a house and everything like that. It was a very easy transition socially for me to graduate school because I knew all these people that were some of my best buddies.

Barr: What made you focus on diphtheria—and why did you become somewhat disenchanted with the topic towards the end or after you finished?

Schiller: I worked on diphtheria by complete happenstance. I was planning to work for someone, who will remain unnamed, and I rotated through this person's lab. It turned out that this professor ruled by intimidation, and it was basically an ugly atmosphere. I was all set to work for this person, who was very prestigious, so I had to scramble for something. Dr. Neil Grohmann, bless his heart, who had been working on diphtheria, was actually involved more in education administration than research in the last few years. He was just getting his research program back up and running. He agreed to take me. I was interested at that point in bacteria—again, I was interested in the more basic aspects of life—and diphtheria got me into the first foray into things that were maybe medically important. My thesis, which quite frankly, wasn't the best thesis in the world—and this is a lesson that you don't necessarily have to have the best thesis to be successful in the end—was studying the way that antibiotic resistant genes got transferred from bacteria on your skin to diphtheria, which infects your throat, but also can infect the skin. It was one of the earlier studies looking at gene transfer for genes that encode antibiotics. I wouldn't downplay it too much, but I had this idea I could do all the genetics and everything that people were doing in model organisms, which we had planned to study. I thought, “Oh, I'll just get this all working in diphtheria.” Of course, I was totally naive in genetics, and diphtheria wasn't worked out until 10 years after I left. I was a little bit over ambitious, but as early graduate students, that's what you learn is what to do—to do tractable things, and not start thinking you can reinvent the wheel and do everything from the start. It was a very good learning experience. I learned, outside of doing my own research and being exposed to very good molecular biology in infectious diseases, that it really set my bar high for what I could do leaving that place. I think that's very important—the atmosphere that you're in sets the level of research you aspire to. There were labs that were doing world class molecular biology on microorganisms at the University of Washington. That was really, I think, the most important thing I learned there.

The reason I got a little bit disenchanted was because I like to study the unity of life and kind of make big connections. Bacterial pathogenesis was sort of balkanized. In other words, if you're studying a bacterium, it didn't really relate to the pathogenesis of these other bacteria that were of different types. Everybody was, to me, working in these little pigeonholes, and I was much more interested the bigger picture. And that is why I was attracted to HPV or human papillomavirus, because papillomaviruses have nine genes, and yet they can induce profound changes in cells to make them from virtually normal cells to cancer cells. Well, at the time, we didn't have the tools to interrogate the whole human genome with its tens of thousands of genes, but here we had an organism with just nine genes and at least one of these was making these big changes, so it must be attacking a fundamental process in that cell that was related to cancers. That turned out to be the case. That's what we initially were wanting to explore—to identify the genes and what they do to make a normal cell into like a cancer cell. We were quite successful for ten years doing those types of experiments. We identified two of the three major transforming genes—in other words, the cancer-causing genes of the papillomaviruses. We were working in a bovine model, a cow virus, because at the time, when we started, the types that cause human cancer weren't identified. It was just about the time that we started our work that the two types that cause 50% of cancer were identified. One of the pivotal moments of my career was the second lecture I went to in January 1983. It was Harald zur Hausen, who later got the Nobel Prize for this. He came to the NIH and said, "I found these two new viruses in 70% of cancers." This basically then transformed what we were thinking about doing, from just studying a model of how normal cells can become cancer into studying a human pathogen that looks like it was going to be responsible for a large proportion of a very important cancer, cervical cancer, worldwide.

Barr: Can you speak a little bit about what enticed you to come to NIH's Laboratory of Cellular Oncology as a National Research Service Award (NRSA) postdoctoral fellow, and describe your relationship with Dr. Douglas Lowy, whom you've collaborated with for decades at this point?

Schiller: The reason I came to Doug's lab is that I knew that my Ph.D. was going to get me necessarily into the best of the most established labs in the world. There was the Fred Hutchinson Cancer Research Center, which is still in Washington. They had a lot of good people who were studying tumor viruses. I asked everybody that was there the same question: "Who is a really good young and coming up researcher in this area, and a really good person?" There were always a couple of names here and there, but at the top of everybody's list was Doug Lowy. It was like a no brainer, so I wrote him. At the time, he really just starting on papillomaviruses. He hadn't published much on it. He was studying how some mouse viruses cause leukemia. At the time, it was really an interesting thing because there were strains that were very similar, and some caused leukemia, and some didn't. I thought that sounded like an interesting thing to study. I wrote a proposal and asked if I could come to his lab to do this. He was impressed that I had written a full proposal that actually made sense. He goes, "I got a position, why don't you come?" But he also said, "Well, in addition to these mice leukemia viruses, we're studying papillomaviruses." I went, "Papillomaviruses? What are those?" I didn't know much about them. Then when I started looking into that, they had cloned the genome of a bovine one, and we knew that it caused this molecular transformation of normal cells. This was a rich area where there was so much to be learned and so little that was known. Of course, I wanted to work on that. It was a growth area. It was just starting because molecular biology gave us the tools that we could really interrogate what was going on. That's why I came to the NIH. The other thing was I wanted to live on the east coast. Because I lived in the Midwest and the West Coast, I figured I should live on the East Coast, at least for a few years, as a postdoc. Of course, what happened then is that when I got to the NIH, I looked around and went "This is a really good place to do research, and if they're not going to kick me out, I'm not going to leave." And they never kicked me out, so I'm still here 35 years later.

Barr: Can you explain about some of the early biological discoveries you made in terms of papillomavirus, the importance of L2 and L1 proteins, and the furin cleavage site that are important to understanding the basis of how the vaccines later worked?

Schiller: For the first ten years, we basically studied how the virus causes cancer and how it replicates and gets expression of its own genes in collaboration with cellular genes. There's the basic molecular biology of the virus. And then it was getting to be about ten years since Harald zur Hausen and his colleagues had discovered that these viruses cause cancer. We knew that it was sexually transmitted, so the virus wasn't acquired at birth or something like that. There's this opportunity—you didn't have to be Einstein to figure, well, if you had a vaccine, that could prevent the infection of the sexually transmitted disease. If you vaccinated before the person became sexually active, then you wouldn't be getting the cancer. Almost all cervical cancer, and a large proportion of oral and anal cancers as well, are caused by HPV. The concept was pretty simple: prevent the virus infection, prevent the cancer. But the execution was kind of lagging.

The virus is actually quite simple in terms of its structure. It's got a major protein called L1, and there are about 360 copies of this protein. It's got a minor capsid protein that's important for infection. But it's only got, at most, 72, so that's why it's called the "minor." People had taken this major capsid protein and tried to make a vaccine with it, but it hadn't been successful in animal models. The reason that everybody was working in animal models is because HPV is tough. It's completely species specific and only replicates and causes disease in humans, so if you want to look at prevention of infection and disease of a papillomavirus, you had to use an animal model. The other problem was that there was no source of HPV virions because they didn't grow in cultured cells. Often viruses like, say, measles viruses or SARS viruses, can be put in tissue culture, cells growing in dishes, and you get virus out. HPV didn't do that. It's got a complicated lifecycle. There was no source of virions, so people made proteins in bacteria and when they used them, it didn't work as a vaccine. We got to thinking that maybe the problem was that the conformation, the shape of the protein that you're getting out of bacteria, isn't right, and that it doesn't match what's on the surface of the real virus. We had the idea that we should make something that looks like the outer shell of the virus but isn't infectious because it doesn't have the virus genetic material, which happens to be DNA in this case. To make a long story short, we were able to generate structures by just expressing this major capsid protein L1 in other types of eukaryotic cells, cells that were more closely related to human cells than bacteria. And lo and behold, we got these structures that look like virus. But that was only first part of the solution.

Just because it looks like the virus, doesn't mean it can generate antibodies that bind to the real virus. And so, we had to prove that. The first thing we made was what we call "virus-like particles." I'll call them "VLPs" for short. These VLPs were a bovine model. The reason we did this is because Doug, before I came, had developed a system where you could measure bovine papillomavirus (BPV) infection in cells growing in the dish. The ability to make them look like cancer cells and pile up so you can count the number of piles of cells—we call them "foci"—measures an infectious event. You couldn't do that with HPV because you didn't have virions, and if you took the DNA and put it in cells, it didn't do anything that was easily scored as an infectious event. When we did this for BPV, it worked beautifully. I mean, the story is that a postdoc did this—Reinhard Kirnbauer, who was a dermatologist by training, just like Doug. We told him to look for these particles, which we saw were assembling in insect cells. We didn't even purify the virions. We just took these insect cells and these particles that we could see in the electron microscope and just injected them into rabbits. And we said, "Well, dilute the sera 100-fold, and then mix it with the virus and see if you block infection." At 100-fold, there was complete blocking of infection. We hadn't reached what's called an "endpoint,"—we didn't know how much you could dilute the sera and still block infection. So, we told them to dilute in the next assay 10,000-fold. Even at 10,000-fold, we still got a complete blocking of infection. Each of these experiments takes about a month because it takes a while for the piled-up cells to appear. We eventually had to go to a million dilution. At a million, we finally diluted it so much

that we couldn't get blocking of infection. The neutralizing titer was 100,000, which was way above what anybody had seen with any other types of viruses. This vaccine has basically exceeded all reasonable expectations at every point in its development. And it's been really fascinating to try to understand why it worked so well. That's been a big portion of my lab work, and it started out from the beginning with unusual expectations.

Barr: Can you speak a little how the vaccine went from being part of your studies to being manufactured as a quadrivalent vaccine, called Gardasil, manufactured by Merck, and a bivalent vaccine manufactured by GlaxoSmithKline (GSK)? What are the similarities and differences between these two?

Schiller: Before we could interest companies, we had to solve a major problem. That's when we tried to do the exact same thing with HPV 16, which is the type that causes the most cancer—about 50%. Obviously, we want to make these VLPs. When we tried, we found that the VLPs looked bad. When we injected into rabbits, the sera didn't inhibit HPV 16 infection. We had developed an assay for HPV 16, but the VLPs just didn't work like the BPV. There were two possibilities. One is that HPVs, which are not closely genetically related to BPV, just do things differently in terms of their assembly, and it wasn't going to work. The other possibility was that the clone of the HPV 16 genome that was being used by everybody was isolated from a cancer. As everybody knew even then, cancers are very genetically unstable. We thought there's maybe a possibility that it's a mutant. The reason that it doesn't assemble is because there's some mutation that occurred during the carcinogenic process in humans. What we did was took a type that was closely related to HPV 16, but infected rhesus macaques—in other words, monkeys. It was quite closely genetically related. When we did that, it worked beautifully, just as good as BPV. We thought, "Ah. It's not because it's a different class, it's because it's a mutant." We asked people at the German Cancer Research Institute, which is where Harald zur Hausen worked, for isolates that were isolated not from a cancer, but from an infection that was benign. We had several different clones from there and they all work beautifully. That's how we solved this problem why HPV 16 wasn't working.

Once we had that, then we went around to just about every major company who did vaccines, at least in the United States. We personally went there and talked to them. The basic response was, "Well, your data looks great—we wouldn't want any better data—but we just don't believe that vaccines against sexually transmitted disease are ever going to work." The reason they thought so is that other vaccines they tried against chlamydia and herpes and other sexually transmitted microbes just hadn't worked. The idea was that if you have an infected partner in a stable relationship, then you may prevent infection the first 49 times that you have sex, but the 50th time you're going to get transmission. For cervical cancer prevention, if you prevent transmission for a month, and now you're going to get cervical cancer at 55 [years old] and one month, versus 55 and zero months. From a public health point of view, it's not going to make any difference. People could not get their head around the idea that it could induce long-term sterilizing immunity, which, in fact, it does. It's actually, in terms of protection, better than just about any vaccine we have. If you're not infected before you get the vaccine, and you get vaccinated as a kid, you have almost zero chance of being infected by the vaccine types—protection is like 99%. It was a leap of faith that a vaccine could to do that.

Two companies, actually, then took that leap of faith. One was Merck, and the other was initially a local Washington area company called MedImmune. They developed the vaccine to phase one trials, which were quite successful. In phase one trials, you just look to see if it induces the immune response that you want. They don't involve showing that it works to prevent infection in this case. And then they sold the rights, which they had licensed from us, to GlaxoSmithKline. What they did is mixed it with their proprietary adjuvant, which is something that increases or potentiates the immune response to a vaccine. They had a special adjuvant, and they developed what was called the bivalent vaccine, which was against the two cancer types, 16 and 18, that caused 70% of cervical cancer. Merck decided that they would use just the garden variety adjuvant, which is just

an aluminum salt. That's like what's in some of the Hepatitis B vaccines and in diphtheria or tetanus vaccines—it's just the standard thing. But in addition to these two cancer types, they included VLPs of the two types that cause 90% of genital warts. In the clinical trials, they looked for prevention of not only infection by the cancer-causing types in generation of precancerous lesions at the cervix, but they also looked at prevention of genital warts. GlaxoSmithKline didn't look for prevention of genital warts because they didn't have those types in their vaccine. We didn't know if the vaccines were going to work in terms of efficacy, even though they generate the immune responses as good as we could hope for. The first results came out at a meeting down in Brazil. I was chairing the session, and Laura Kowalski was in charge of this very early Merck trial where they just had one type, HPV 16. When they looked at who got infected comparing controls and those who got the vaccine, the score was like 42 to one, so there was almost no infection from the very beginning in the people that got vaccinated. Right then, I turned to the audience and said, "You know, ladies and gentlemen, you've just seen history." Because in my mind, this meant that the vaccine was going to work. Now, there are a lot of skeptics, and somebody got up and said, "No, this is pre-history"—in other words, you've got to do a lot more to prove it. In some ways that was true. But in my mind, it was going to work. Now it was just a downhill slope, doing larger trials and showing that you not only prevent infection, but also these pre-malignant lesions that are subject to treatment so that women don't get cancer. The bigger trials then subsequently demonstrated that. It's almost 100% protective against precancerous lesions by the types in the vaccines. In these trials, you can't let anybody get cancer, because in screening, you identify the premalignant lesions, and they have to be removed, ethically. Also, if you wait for cancer, you'd have to do the trial for 20 years, because it takes a long time between when you get the infection, generally, and when you get cancer.

Barr: Will you talk about what it was like to have your own daughter get vaccinated? That must have been very exciting for you.

Schiller: It's actually quite interesting. The timeline of this vaccine was way longer than the SARS vaccine. Fortunately, the COVID vaccines got developed much more rapidly. It took about 13 years to develop the HPV vaccine from the time we made the initial discovery that these particles can assemble and induce very high titers of infection-blocking antibodies. During this time, when my kids would say what their dad does, they would say, "Oh, he develops the cancer vaccine." I said, "No, no, I developed the anti-cancer vaccine. It's not the cancer vaccine. You have to say it was the 'anti-cancer vaccine.'" But it was very gratifying that just at the time when she was 13 and ready to get this vaccine, it became available. The Merck vaccine was licensed in 2006, so I was able to go with her to our local clinic and she was very proud. She said, "Hey, this vaccine I'm going to get, my dad invented this vaccine." They were going to do it on TV, but for some reason, there was some mix-up or something and they didn't do it on TV. But I was deathly afraid that she was going to go, "Ow, ow, ow" or faint or do something like that because she was getting an injection. Of course, she didn't, she was smiling and perfectly happy through the whole thing. I have a picture of her and me, holding her hand receiving the vaccine. Early on when people would say, "Well, do you think this vaccine is safe?" I would show them the picture and I didn't have to say anything.

Barr: That's the most rewarding of all for you probably.

Schiller: Yes.

Barr: Can you talk about the research into the cross-protection of this vaccine for other types of HPV not targeted? As you discussed, most are geared towards HPV 16 and HPV 18, but there are other kinds.

Schiller: Type 16 and 18 account for about 70%, and then there are about five other types that count for another about 20%. The Merck vaccine, which contains the simple immune-stimulated adjuvant, doesn't seem to induce

hardly any cross protection against other types. Based upon this, they came up with a second-generation vaccine, which has VLPs for these next five types that cause cancer. Given that it's type specific, basically, it can protect against about 90% of the types that cause cancer. That is called the nine-valent vaccine. That's actually the only one that's available in the United States now. A lot of the world is still getting the four-valent vaccine, and to some extent, that two-valent vaccine from GSK. Now, the GSK vaccine, probably because it's got this special adjuvant, has some degree of cross protection, although it's not complete. GSK now is developing next generation vaccine with another company from China called Inovax—where they were going to have a nine-valent vaccine as well—but it's going to have this special adjuvant. There has been a bit of an arms race to include more types so that you get protection against more and more of the cancer-causing types.

Barr: Can you speak about some of the subsequent studies of the vaccine, such as looking at its effect on menstruating women versus those using contraceptives, or at pregnancy and miscarriage among those who use the vaccine?

Schiller: It's been given to women at all stages in their menstrual cycles, and on various types of contraceptives or not, and it doesn't seem to affect the immune response or the safety of the vaccine. Also, people have looked very closely at whether there's any sort of signal that it could have any effect on reproductive health. Really there's no signal whatsoever that suggests that it has any effect on reproductive health. When you think about it, all this is, is like a ball of protein that you're putting in somebody's arm. The amount of perturbance to the immune system is much less than anytime you have a common cold. It's not like something that replicates or anything like that, so the chances of causing major adverse effects were very low from the beginning. But it certainly has been looked at closely, and it's considered a very safe vaccine.

Barr: Can you talk about some of the studies that have looked at whether the vaccine would still be beneficial for those who have received treatment for HPV in the past or those who currently have it? There have been a lot of studies around that topic.

Schiller: In the initial studies and subsequently, it's pretty clear that if you have an infection and you get vaccinated, it doesn't make it go away. Or it doesn't influence the progression to precancer. In other words, it doesn't have a therapeutic effect. Having said that, there is some evidence that if people have a lesion and it gets removed, and you vaccinate that person, the chances of her getting another high grade precancer that needs to be removed is lower. But we think the reason for that is that it prevents new infections. That woman who had that lesion, she may be more susceptible to have infections progress to precancer than the average woman. She had it by one type, now she may have it by another type. If she's still at risk of getting infections, it makes sense for her to be vaccinated. But we don't think it has anything to do with getting rid of residual disease or residual infection. It's really still working at the level of preventing new infections.

Barr: What are your thoughts about one dose regimes for HPV as has been tested in the Costa Rica trial? Would you speak about your efforts in determining the efficacy of all different dosing regimens, from three, two, and one?

Schiller: This is a really interesting story, because it goes back to the fact that, although two of the companies that are among the best drug or vaccine developers in the world, Merck and GSK, were independently doing this, NCI decided to run their own trial. Doug and I were instrumental in getting this going and participating in it. There were two main reasons to do it. One, we thought it was too important not to carry it through, and companies can pull the plug, for whatever reasons. They may just decide they are going to do something else. And the other thing is that we were going to ask questions that weren't in the companies' interest. The companies want to do the minimum that they have to do to get licensure. And that's reasonable, they want to

get it as soon as possible. They don't want any data that confuses things. What happened in their studies is that everybody was supposed to get three doses. If you didn't get three doses, well, then you're out of the study. They didn't really follow you up to see what happened. I mean, they had to follow them for safety, but not for efficacy.

NCI decided that we would do a trial down in Costa Rica, because we had infrastructure to study HPV natural history there, and we've been working with the Costa Rican government to study HPV and its cause of cancer for a long time. One of the things that we did was we kept following the people who didn't get the prescribed number of doses, the three doses—just got two or just got one. And it turns out that now, after 11 years, there is no difference. We can't see any difference in the protection against HPV infection or disease from the women who got one dose versus three doses. When we first reported this, at the end of four years, this was kind of an eye opener. People said this wasn't formally randomized. It wasn't like some people were destined to get one dose, and some got three doses, it was by happenstance that they only got one dose. The level of proof is considered substandard, but it certainly is a hypothesis-generating finding, so other people started looking at the question. There was a study that was done by the International Agency for Cancer Research, an arm of the WHO [World Health Organization] in India. They decided to look at their one dose efficacy too. It turns out, up to 10 years, there's no difference in protection from one dose and three doses. This was very surprising because there are no licensed single dose subunit vaccines. The VLP is just a glob of protein and it's not a replicating attenuated virus. Well, that has not been seen, where one dose gives strong protection, so it was totally surprising. But since then, there's been some randomized trials.

There was a study in Kenya that just got announced at an HPV meeting in Washington a week or two ago, where, in 15- to 20-year-old girls, both the nine-valent Merck vaccine and the GSK vaccine gave better than 98% protection against persistent infection by the types in the vaccines. You can't do much better than that. If we get 98% with one dose, there's not much of a space for two or three doses to do better. Based upon this data and some data from effectiveness studies, where people actually look in populations at what happens if girls who just got one dose in vaccination programs versus two or three doses, if restricted to the girls who clearly were young when they got vaccinated—so they didn't have infection before they were vaccinated—again, it looks like there's no difference between one, two, or three doses. Based upon this, there was a very important decision by the WHO just this last year—we've been trying to accrue the data to make WHO and other regulators comfortable with this—that said that one dose gives high level efficacy and is basically equivalent to two doses. So, give two doses if you want, but we endorse one dose. Based upon this, and their own evaluation of the data, a relatively large number of countries are going to one dose. This includes the UK and Australia, who have one dose programs right now, but also major countries that don't vaccinate anybody yet, such as India and Nigeria, who have large populations and large problems with cervical cancer. This is going to probably be a real watershed in terms of delivery and increasing uptake of the vaccine. Despite the fact that it's been available over a decade, worldwide only about 15% of girls get the vaccine by the time they're 15. In low resource settings, it's only about 3%. And why that's important is that most cervical cancers—90%—happen in low resource settings. Why is that? It's because they don't have access to the good screening programs that we have here in United States. In the United States, screening has decreased cervical cancer by more than 80%, so it's not a major cancer in the United States, because we already have what's called secondary prevention—identifying the infections before they become cancer and cutting them out. That's why we really need to increase uptake in low resource settings. We think that, by far, the best way to do this is to just give one dose.

Barr: Are you worried at all about the role of societal values or norms in the uptake of these vaccines in some of these places around the world? Some of it is because there's limited resources, but there are sometimes other ideas around certain vaccines, especially with sexual health and girls.

Schiller: To put it in broad strokes, there's been more of a problem with vaccine hesitancy in high-income countries where they have access to the vaccine. In low-income countries, overall, if they can get the vaccine, they embrace it. There are countries like Rwanda, who immediately were at 90% coverage. The ironic thing is that rich countries can have the vaccine, but a lot of people don't want it, and poor countries can't access it. If they get it, they use it and get high coverage. It's not 100%. But generally, that's the case—they believe in the vaccine, there's much less vaccine hesitancy in lower resource settings. They want the vaccine, but they haven't been able to get it, both because there's been a shortage of the vaccine—which can be overcome by having one dose vaccination—but also, it's just been very expensive. It's not only expensive in terms of buying the vaccine, but because of the implementation programs. Unlike childhood vaccinations, which are well established, and babies are going to the clinics, this is basically a new adolescent health care platform where you have to get adolescents into the clinics, or in school-based vaccination. Developing these new platforms for an intervention is costly and time consuming.

Barr: Since the initial vaccines came out in the early 2000s, you and your lab have continued doing a lot of other research, which includes discovering the pathway through which papillomaviruses infect cells, the fact that human papillomavirus preferentially binds and infects tumor cells rather than healthy tissue, the interaction with distinct post components on the basement membrane, how different ways of administering the vaccine can induce tissue resident memory CD in T cells, and looking at heterologous boosting. Can you speak about some of these areas of interest and how you feel they will influence next generation vaccine designs and potential therapeutics?

Schiller: There's a lot of questions there. But to start out, because it was so surprising that one dose of the vaccine worked, it was important to provide biological plausibility—so how come this vaccine works at one dose where other subunit vaccines have failed at one dose—because it provides confidence that what we're seeing is real and robust. We studied it in terms of the immune response to this vaccine. It turns out that this vaccine is unusual in that the blood level of antibodies induced by the vaccine drops initially, but then, from year two to now, for 16 years, it just stays flat—it stays the same. It doesn't continue to fall, so people remain protected indefinitely. We've been trying to understand, in terms of immunology, why that is the case. We think a lot has to do with the structure. We talked about these VLPs. We think that this structure is important for the ability to induce this type of antibody response that lasts indefinitely. I won't go into why we think that. The other thing is, we think that the virus is unusually susceptible to low levels of antibodies that are floating around in the blood. To show that, we had to figure out how the virus infects its normal tissue, like cervical vaginal epithelium, and how antibodies prevent it. What we found is that antibodies that have such low levels that you can't measure it in the test tube actually work in animal models and, presumably, in people. We discovered alternative ways in which the antibodies can prevent infection. And again, I won't get into the details. But now it makes sense that even women who have very low levels of antibodies are protected, because the virus is just super susceptible to these antibodies.

The second part of your question is about therapeutic vaccines. There are still a whole lot of women who haven't been vaccinated, and girls who won't be vaccinated, who will acquire infections. A therapeutic vaccine that would work to get rid of that infection, or premalignant disease, could do a lot of good for them. People have been working on this basically as long as the prophylactic vaccine, and a lot of different ways have been tried to do this. Mostly during the development of these precancers and cancers, there are two genes—two of these oncoproteins—that are selectively retained and expressed, and so they become non-self-targets for therapeutic vaccines. They're very attractive targets for developing vaccines against. But so far, none of the ways that have been tested—and multiple academic labs and by multiple companies have attempted to do this- has worked well enough that it led to a commercial vaccine. People first started with cancer, and they basically had no effect. Then people mostly have gone down to precancer, and they may see a significant but small effect, like

rather than 5%, spontaneous loss, they have 20% or 25% spontaneous loss. The difference is never much more than about 20% more loss of infection. It's not like the prophylactic vaccine, which induces almost 100% percent prevention. There are already good ways of treating these lesions, so the bar for a prophylactic therapeutic vaccine is high. We think that part of the problem is that the immune response they're generating is systemic—it's floating around in the bloodstream—while the infection is local in the epithelium, the covering of the cervical vaginal tract. The trafficking of these systemic immune cells to the local site may be a limiting factor. We're trying to increase their expression locally by using vectors—inactivated viruses like HPV or adenovirus—to generate immune responses that are more local, and that we think will work better. We've been working with Janssen on an adenovirus for a long time. It got interrupted because of the COVID situation, so that's been put on hold. But we think there is still potential for a therapeutic vaccine that could do a lot of good for a lot of people.

Barr: What are some of the other questions about HPV that your lab continues to investigate presently?

Schiller: Well, we're studying in more detail how the infectious process works as a basic cell biological and virologic process. We have also been trying to understand why these virus-like particles, or the viruses themselves, don't bind to intact epithelium. They initially have to bind to something that's called a "basement membrane," which separates the skin layer essentially from the underlying layer of the tissue. But what they do is, surprisingly, bind to almost all cancer cells, but they don't bind to the normal tissues. This makes it quite obvious that these particles can be used as guided missiles to deliver drugs specifically to cancer cells. We're very interested to understand why there is this evolutionary drive for cancer cells to get the same kind of molecules that the virus binds to as what's normally restricted to this place between the two compartments of skin. Why do they do that? What are the changes and what's the evolutionary drive? We're investigating that as a basic sort of cancer biology, because again, this gives you some insights into common features that you may be able to attack on a wide variety of cancers.

What we've done initially—and we're doing this as a long-standing collaboration with a company called Aura Biosciences—is we took the virus-like particles, which is the same basically as what's in the vaccine, and we put a dye on them. Now, what's interesting about this dye is that if you shine an infrared laser, which is like a red color, on to the dye, it changes and reduces what we call "reactive oxygen species." These are things that react with a bunch of different aspects of the cell, and basically kill the cell. So now we have these virus-like particles that are decorated with the dye, and they're sticking to the cells. All of this damage, this release of reactive oxygen species, is taking place right next to the cell membrane. They punch holes in the cell membrane and kill them instantaneously. The guts spill out and this induces an immune response against the tumor. This worked really well in our animal models and Aura has gone ahead with clinical trials. They're about to start a phase three trial of these dye conjugated particles for ocular melanoma, which forms in the space behind the retina in your eye. Current treatments are quite damaging to the eye, so we're trying to do something that's safer, so we can start treating earlier before other treatments are used. If you wait too long, it's hard to tell whether they're cancerous or just a mole, and people go on and get metastatic disease and die for it. We're also using the same technology, the same particles, starting now with a phase one initial safety study in bladder cancer. But because these particles bind to all different types of cancer, the sky's the limit in terms of what we can potentially use—as long as they're fairly superficial, because these infrared lights don't penetrate very far in the skin.

Barr: Can you speak about how you've used some of the lessons learned with HPV towards other diseases like HIV?

Schiller: We haven't worked specifically with HIV, but people now are trying to generate broadly cross-reactive antibodies against HIV. We think that some of the things we've learned about the immune response to these

virus-like particles may help develop a more effective HIV vaccine in two ways. One, I talked about the durability of the response—that when we get the response, it lasts forever. That's what you want for HIV as well. The other thing is, we think that the diversity of the antibody responses to a virus-like particle, which has many copies of the same peptide around the surface, is greater than the diversity of antibody responses to a simple protein that's just sort of floating around. Again, by increasing the diversity of the antibody response, you increase the chances of generating some of these broadly cross-neutralizing antibodies. People are working on virus-like particle vaccines for many diseases, based on the HPV vaccine working so well and what we've been able to show with HPV. For instance, for COVID, the initial vaccines were all mRNA, because they were just the easiest to make, and they're easy to change. But my guess is that people are working on virus-like display vaccines, so like the HPV vaccines, that are going to generate higher and more durable levels of antibodies, and eventually will replace them. People are trying to develop vaccines against Epstein Barr Virus (EBV), using virus-like particle display. It's just two examples where how the VLP concept has really been taken over by the vaccine research community. If you want to make antibodies that are diverse and last a long time, there's nothing that we know right now that is better than virus-like display.

Barr: What are your hopes for the Cancer Moonshot Initiative putting more attention on viruses that cause cancer?

Schiller: Well, I don't think the Moonshot specifically has initiatives to do viruses that cause cancer, but there certainly is activity to develop vaccines against other infectious diseases that cause cancer. For instance, I mentioned EBV. There are people here, Jeff Cohen and colleagues at the Allergy and Infectious Disease Institute (National Institute of Allergy and Infectious Disease, NIAID), that are developing what looks like a much more attractive EBV vaccine based upon this virus-like particle idea. People are developing vaccines against hepatitis C that hopefully will work. Also, a key one—it's interesting—the microbe that causes the most infection, even more than HPV, is a bacterium called Helicobacter pylori, which causes stomach cancer. It's been a tough thing to develop a vaccine against because it infects the lining of the stomach, and getting the immune response there and knowing what portions of the immune response would work [is difficult]. But that's a very important target to try to vaccinate people against. People are working on this. There probably could be more support, I think, for initiatives in that space.

Barr: Will you comment on how being part of the NIH Intramural Program has shaped and accelerated your research?

Schiller: It's really been an extreme blessing to be able to work in the intramural research program because it’s allowed me to do what I want to do. As a great illustration, when we started to develop these HPV vaccines, neither Doug nor I had any experience whatsoever in vaccinology, immunology, or even studying the virion proteins. And if we had been at a university and applied for a grant to do this research, they would have laughed at us [and said], “You’re just throwing it away—you guys are doing a really good job at studying how viruses cause cancer, but what are you talking about? You have no experience in this. You can't do that.” But in the intramural program, we basically do what we want, and then every four years we have to justify it. It's mostly a retrospective review. We have to justify what we're going to do to some extent, but it's mostly evaluated on what we've done. And of course, by the time we got reviewed for this, everything was working beautifully, so everyone said, “Of course, that was a great idea, we really support that.” But we never would have gotten support beforehand. Recently, I've been getting into cancer therapies where we're trying to recruit preexisting antiviral immunity to treat cancers with the idea of developing broadly applicable therapies that can work in low resource settings. Well, again, we hadn't been working in cancer therapies. There are people who have been—as long as I've been working on HPV on cancer therapies—and they said, “Well, why are they doing it? What are you trying to do, jump into this field?” But we don't have to ask anybody. We just do it, and we think we have a

very promising way of recruiting immunity to cytomegalovirus that could generate a product that could be used to treat cancers in low resource settings. Now, it's early days, it's a high-risk, high-reward type of project. But again, it's not something that we probably could have been funded on from the outside. Now we could, because our preliminary data is good enough that we could get funding on the outside. But we wouldn't have gotten it initially.

I have been changing what I do throughout my career. Probably the best thing and the worst thing about me as a scientist is that I get bored easily. I'm not content to keep following one line of research down into more and more and more detail. I'm going to jump into something else just because it interests me, and I want to try a new idea. Maybe I lack a little bit of follow-through in some things. When you write a grant, you have to keep doing the next step and what you've done before, because that's what you can get funding for. But here, one has the freedom to actually change what is done over time. It really has been energizing for me to change the way I think. Now I'm just completely fascinated with the idea of taking modern molecular medicine and the complexity of it and ending up with simple products downstream for use in low resource settings. I think molecular medicine can really be used to decrease health disparities around the world. Presently, it's mostly increasing it because it's becoming more and more complex. Cancer therapy is now all about personalized medicine—sequencing an individual's genome and pulling out the individual mutations, making a vaccine for that individual, all this sort of stuff. That's great for that individual. But it won't bend the curve of cancer deaths globally. We have to be intentionally thinking about what we want at the end from the beginning—not do the trickle-down effect, where you do things for the rich and you hope it trickles down to the poor. In molecular medicine, I just don't think that's going to work very efficiently. We've got to start with a goal of developing things for low resource settings. And I have the freedom to do that in the intramural program, where I probably wouldn't at a cancer center or in a microbiology department at a university.

Barr: Is there anything else that you'd like to share about your research or about your time at NIH?

Schiller: I just want to thank the NIH and the Cancer Institute for supporting our research for all these years. It has been the privilege of a lifetime to be able to work here.

Barr: Thank you so much for all you have done in your service to NIH and the country.

Schiller: Well, thank you.