A Conversation with Phillip Sharp

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Phillip Sharp is Institute Professor and Professor of Biology at the Massachusetts Institute of Technology and Member of the Koch Institute for Integrative Cancer Research.

Carika Weldon: It's extremely exciting to be talking to the codiscoverer of splicing. How is that for you to be a scientific celebrity?

Dr. Sharp: I try to resist celebrity. It gets in the way of knowing people and doing work. I'm very proud of being able to make that contribution and introducing the world to RNA splicing.

Carika Weldon: When you learn in university about RNA expression and gene regulation, you don't even realize at the time that the person who discovered it is still alive. How is it for you from the other side to see where the field has gone today from where it was when you started?

Dr. Sharp: I was at Cold Spring Harbor for 3 years in '71 to '74. Before that I was at Caltech for 2 years working in bacteria and doing electron microscopy of the DNAs of plasmids and mapping genes on the chromosomes of *E[scherichia] coli*. It was genomics before genomics was called "genomics." I came to Cold Spring Harbor to learn how to work with DNA tumor virus. In those days, the molecular biology community considered working with mammalian cells to be a waste of time. There were a few pioneers: Jim Darnell and a few others. When Jim Watson became director of Cold Spring Harbor, he started the initiative on cancer. It was the period of the "War on Cancer," and I came because I wanted to learn how to work on tumor viruses in mammalian cells. That was the theme that Jim was putting together because these viruses have a few genes that cause tumors in rodents, and we wanted to know how a gene could cause a tumor. So we started working with and studying these viruses.

I began to read about the molecular biology in mammalian cells, and I came across the phenomenon that, in the nucleus of human cells, there was this long RNA called heterogeneous nuclear RNA. It had a poly(A) tail at the 3' end and a cap at the 5' end, so it had most of the modifications we knew about in messenger RNA, but it was five to 10 times larger and no one was paying any attention to it. But I knew adenovirus, when infected in human cells, had the same long nuclear RNA but a shorter cytoplasmic one, and that was something I kept my eye on. I thought, "I know how to solve that problem

for adenovirus." I didn't know if it would tell us anything in general, but I knew how to solve the issue of what that relationship was.

I left Cold Spring Harbor in '74 to go to MIT and we did the electron microscopy of the RNA from the cytoplasm in the cell compared to the DNA in the nucleus, and there were these three beautiful loops. It told us that the long nuclear RNA was a precursor to the cytoplasmic RNA, and RNA splicing was the process that removed the middle of it. That became a paper that was published in '77. It was discussed here at Cold Spring Harbor in the '77 Symposium—which was about chromatin—but the RNA stole the show.

So, the field has grown. It just exploded after the '77 Symposium, because many labs could begin to clone human genes and genes from mice and other species. Here were these introns between the exons that code for the protein that had to be spliced out, and within 6 months everybody who was literate on the topic knew about this discovery of split genes and RNA splicing. It was absolutely a remarkable time.

Carika Weldon: Were people at the time shocked or were they as excited as you were?

Dr. Sharp: They were stunned. Every major lab had data in their notebooks they had been ignoring because they couldn't explain it. Richard Flavell was working on β -globin and he had this restriction cleavage site in the middle of the cellular gene but it wasn't in the middle of the message, so he couldn't figure out why there was this restriction enzyme site. And I said, "Just listen." And then he went home and within a month he had described that there was an intron; in fact, there are two in globin. Pierre Chambon at Strasbourg and Phil Leder at the National Institutes of Health had similar data in their notebooks, and Susumu Tonegawa and Wally Gilbert had sequenced the v-region of an immunoglobulin gene and there was this little region in the middle of the sequence that coded for amino acids that was meaningless, and they couldn't figure out how it was dealt with. Splicing fixed all that.

We're still struggling with alternative splicing, because it varies from cell to cell. Even though we only have 21,000 genes, every one of these genes are spliced in

different patterns by alternative splicing, making different proteins in some cells. Until we got the technology—and that's only the last year or so—to do RNA sequencing from a single cell, we really didn't know what type of messenger RNA was expressed in each of the cells. We know that it makes a difference, because if you perturb the alternative splicing, in many cases you see a change in phenotype. So, even though we're in the genomic era, we're still struggling with the complexity of these biological systems.

Carika Weldon: So there's still science to do. Can you tell us about your recent work?

Dr. Sharp: I'm going to talk about a breakthrough now. It's not my breakthrough; it was done by Tony Hyman at Max Planck in Dresden, Germany and Cliff Brangwynne at Princeton. If you look at a cell through a microscope, you see a nucleolus and you see other dense particles. They recognized that many of those dense particles were membraneless subcellular bodies created by what is called a "phase transition." They have a number of molecules that have valency and they coalesce, and they make a concentrated body. In these concentrated bodies, very important reactions occur. In fact, they are critical for these reactions. They make them work at the rate and pace that they need to work. They can be dissociated and reformed. That's a form of regulation. What I've been working on the last 2 years with colleagues at MIT is how that process is central to the transcriptional process that copies RNA from the DNA. That's your major point of regulation.

Every cell in your body has the same DNA, but some cells are skin cells and some cells are blood cells; they express subsets of genes differently. When you get diseases like cancer, the genes change in their expression level and that causes the growth. That regulation of genes, turning them on and off, involves this condensate process. It's a very important insight because now we're going to be able to pinpoint the signals that come into the cell that turn genes up and down. As we learn about this, we will learn how to control gene regulation. That'll help us to treat diseases that we can't treat now, from cancer to Alzheimer's.

It's really surprising that we've been working on cell biology for all these years and it wasn't until about 10 years ago that somebody made the insight that this whole process occurs. Now it sort of tumbles forward and people learn about it. They each relate their own work to it and it's growing and growing in tempo.

Carika Weldon: You've come from the beginning of this field of RNA splicing. We are where we are now. Technology has gotten better: single-cell RNA-seq, long-read RNA sequencing. Where do you think we will be in another 15 years?

Dr. Sharp: I can't answer that question. I know that anything I say is going to be wrong. If I am here 15 years from now, I'll be dramatically surprised by what's happening. I think we're going to see the integration of intense computing into the modeling and understanding of how cells function. It's clear that the complexity of cells is more than

the mortal mind can deal with. To make progress now, I can't think gene by gene. I have to think about relationships between genes and relationships between genes and the physiology of the body. That's the challenge we're at now. That's going to require the integration of the capacity to compute models that relate systems of genes to phenotypes and to communicate these insights to each other.

We will make predictions and go in the lab to test them. We will work to expand that knowledge, but we need these tools from systems and computational biology to make the next step. I think that's going to happen in the next 10 years, and it will change our vocabulary. It will change how we even talk at symposiums. We're going to be walking through 3D stereographics saying, "That piece of the cell is dynamically interacting with that piece of the cell over there, and it's doing this." It'll look like *Star Wars*, but it won't be "boom-boom-boom, shoot-'em-up." It'll be proteins and genes interacting and changing how cells become malignant, and explaining and making predictions as to how one could intervene with it. It's a totally exciting field.

Carika Weldon: Can you take us back to 1993? That was a big year for you: the year you won the Nobel prize. What was that like?

Dr. Sharp: Breathtaking. The way prizes work in science is that you get them early in your career if you have done noteworthy work. When you look who had won before and one in four of the people who had gotten *that* prize also got the Nobel prize, you get the feeling that you might be on a list somewhere. I had gotten a number of those prizes with Tom Cech. Tom discovered self-splicing: that the RNA in some introns catalyzes its own excision. He got the Nobel Prize with Sidney Altman in Chemistry in 1989. I assumed that the Nobel committees had recognized splicing.

So, I had sort of relaxed on Nobel Day. I was in bed sleeping in a little late and the phone rings at 6 in the morning. And I said, "Who's calling me at 6?" So I pick up the phone and it's a Swedish colleague who had just come out of the committee meeting and said it had been announced that I was chosen as a Nobel Laureate that year with Richard Roberts. I took a minute to digest this. Then he asked me if I had the telephone number of Rich Roberts, because they didn't have it. He had just moved from Cold Spring Harbor up to New England Biolabs. I tried to find it, but after I called my wife and she responded and jumped out of bed, I said, "You're going to have to find it somewhere else." I had just no chance. I'm not going to be able to do anything.

So, the day just unfolded like that. I get a call from MIT wanting me to be there at 10 in the morning for the press conference. And I go and I have some champagne with my assistant and then I have the press conference, I have champagne. I go to lunch with the Dean, I have champagne. Go to the department. I have champagne. I go home, we have a block party. I have champagne.

Then I go home and the Dean of Science at MIT calls and says, "We want you to talk at 2 in the afternoon about

A CONVERSATION WITH PHILLIP SHARP

3

what you did to get a Nobel Prize. And I said, “Who am I going to be talking to?” And he said, “Well, we’re going to advertise it to all of MIT.” Seventeen thousand people. Actually, about 600 people showed up and I had to put together a very general talk about the subject. It turned out

to be one of the most pleasant, exciting moments: to share it with those people who knew me but didn’t know the work, but were so excited about MIT and a faculty member getting recognition. Really, a wonderful time. If you get offered a Nobel Prize, say yes.

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