Europe Medical

Born in Toronto, Canada, Shirley Tilghman majored in chemistry and biochemistry at Queen's University in Kingston, Ontario. She earned a Ph.D. in Biochemistry from Temple University in 1975. As a postdoctoral fellow at the National Institutes of Health, she helped clone the first mammalian gene (β-globin) and began to ask questions about the molecular basis for embryonic development. After her postdoc, she was a researcher at what is now the Fox Chase Cancer Center in Philadelphia. In 1986, she moved to Princeton University, where she made seminal discoveries about "imprinted" genes, genes that are expressed differently depending on the parent from which they are inherited. She was the founding director of the Lewis-Sigler Institute for Integrative Genomics. Dr. Tilghman was the president of Princeton from 2001 to 2013. She is a member of the National Academy of Sciences and serves as a trustee for multiple institutions.

An Interview with Shirley Tilghman

How did you get interested in science, and in biology in particular?

It began with loving math. My father claims that when I was five, I wanted to do mental math puzzles instead of having stories read to me! In high school this evolved into a strong interest in chemistry because I loved the logic of chemistry—the rules. But in college I realized I was unlikely to be a good chemist because it wasn't coming naturally to me. I went looking for something more compatible with the way my brain worked and happily stumbled upon the Meselson-Stahl experiment [see Figure 16.11], which I thought was the coolest thing I had ever read. I barely knew what DNA was, but I knew I wanted to learn about it! I wanted to be a molecular biologist.

When you set up your own molecular biology lab, how did you choose what to study?

I wanted to study how genes get turned on and off during early mammalian development, so I went looking through the literature for a messenger RNA that was expressed very early at very high levels and was regulated. I stumbled on the α-fetoprotein gene, the *Afp* gene. It's turned on early in fetal development and is one of the most abundant mRNAs, but is completely shut off after birth. We learned that it is the enhancers of this gene—the DNA sequences that transcription factors bind to—that make such high levels of gene expression possible during specific stages of development.

How did your work on regulation of *Afp* lead you to study the *H19* gene?

This was a classic case of serendipity. If you've seen the children's book *Little Bunny Follows His Nose*, that's how I think of the *H19* gene. When we were working on *Afp*, we wanted to find other genes regulated in the same way, and *H19* was the most dramatic example. The first thing you did then when you got a gene was to sequence it, and that's what my graduate student Vassilis Pachnis did. He brought the sequence to me, and I could see that there was no region in it that coded for a protein, so I asked him to sequence it again. That poor guy sequenced *H19* probably ten times! What finally convinced us that the gene's product was a "noncoding RNA"—an RNA that didn't code for a protein—was sequencing the same gene from multiple mammals. We saw that the sequence was very similar in all of them, but none of them had a sequence that coded for a protein. *H19* was the first gene for a noncoding RNA ever found!

What else did you find out about the *H19* gene?

When we were working on *H19*, I had a classic science experience. I went to a scientific meeting and met a researcher who had reported "imprinting" of the *Igf2* gene, which is near *H19*. Imprinting means that only the copy of the gene inherited from one particular parent is expressed. There were many parallels between *Igf2* and *H19*, so I ran back to the lab and convinced a postdoc named Marisa Bartolomei to do an experiment to determine whether *H19* is imprinted. We discovered that only the copy of the *H19* gene inherited from the mother is expressed—in other words, *H19* was imprinted also. We spent the next ten years working out the details. This was the first imprinted gene where the mechanism was unraveled. It turns out that imprinting involves adding methyl groups to the DNA that affect expression of the gene—the methyl groups are only added in the gamete from one parent, either the mother or the father. At least 100 genes are now known to be imprinted, and there are even more candidate genes to analyze.

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Dr. Tilghman and graduate student Ekaterina Semenova examine a mouse tissue preparation.