# QnAs with David Baltimore

At the age of 37, David Baltimore accomplished what many researchers dream of but few achieve: reversing an entrenched dogma, eventually leading to a new view of life. In the early 1970s, Baltimore, a member of the National Academy of Sciences and a professor of biology at the California Institute of Technology, discovered reverse transcriptase—an enzyme found in some tumor viruses whose genetic code is written in the RNA alphabet. He found that reverse transcriptase can copy RNA into DNA, indicating that some viruses replicate via a DNA intermediate. The finding, which won Baltimore and others the 1975 Nobel Prize in Physiology or Medicine, enriched biologists' views on the direction of flow of genetic information in cells. Baltimore was the keynote speaker at the Sackler Colloquium, "Telomerase and Retrotransposons: Reverse Transcriptases That Shaped Genomes," held in September 2010.* Here, he offers PNAS readers his perspectives on reverse transcription.

**PNAS:** Researchers are finding ever more roles for reverse transcription in cell physiology. Did you envision diverse roles for the enzyme when you first discovered it?

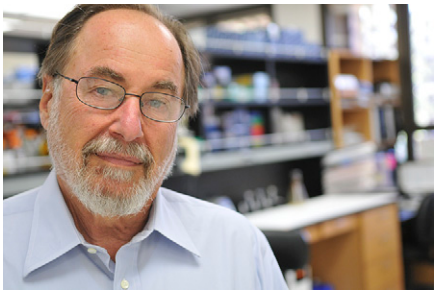
**Baltimore:** All we knew when we first discovered the enzyme was that it was found in viruses. We had no idea whether there was any cellular counterpart for the enzyme or if there was a physiological system that used reverse transcription. We certainly didn't imagine telomerase [a reverse transcriptase implicated in aging in people]. However, because reverse transcription is such a fundamental biochemical process, we suspected that the enzyme might have other roles. HIV came along about 10 years later.

**PNAS:** The discovery of HIV-1 reverse transcriptase led to antiretroviral therapies for AIDS. Which other diseases might become tractable in the coming decades, thanks to our growing knowledge of reverse transcription?

**Baltimore:** We have not found reverse transcriptases in human disease-causing retroviruses other than HIV and HTLV. But there are a number of diseases that seem to have an infectious component that we don't understand. For example, no virus is unequivocally associated with multiple sclerosis, but perhaps there's a retrovirus hiding there. We just don't know.

**PNAS:** Can reverse transcriptases shed light on evolution?

**Baltimore:** Reverse transcriptases are a major evolutionary force. A lot of genome shaping is a consequence of reverse transcription. Their ability to copy genomic



David Baltimore.

elements and their mutagenic activity as they move around the genome make them important to evolution. Reverse transcriptases can copy messenger RNAs and reinsert them into the genome as pseudogenes. There's increasing evidence that pseudogenes affect cellular physiology.

**PNAS:** The human genome is littered with what has been labeled "junk DNA," a great deal of which seems to be the product of reverse transcriptases. Do you think these are largely parasitic DNA sequences?

**Baltimore:** A lot of the repetitive DNA in the genome is parasitic. But there is increasing evidence that evolution has coopted some of that parasitic DNA and used it to shape the genome. I've always been struck by the fact that some organisms have very little parasitic DNA and others have a lot, which suggests that this DNA might not play a fundamental role.

**PNAS:** You've worked on viruses for much of your career. Has your view of viruses within the tree of life changed over the years?

**Baltimore:** I started in virology before there was any knowledge of genome sequences. Viruses were truly a black box. Once the sequences became available, the first thing that struck us was the differences among viruses—and the lack of obvious evolutionary links between them. That's partly a consequence of the highly mutagenic nature of viral polymerases, which replicate viruses, and the vast number of replication cycles that viruses go through over evolutionary time. Later, when sequence information for individual viral genes became known, such as the genes in HIV, the field of virology took off. Also, the viral world continues to expand over time—in nature and number. Take huge viruses, like mimiviruses, for example: we could never really have imagined them before actually seeing them.

**PNAS:** Which of the findings presented at the 2010 Sackler Symposium, "Telomerase and Retrotransposons: Reverse Transcriptases That Shaped Genomes," surprised you the most?

**Baltimore:** To me, the most surprising finding was the structural complexity of telomerase (1)—especially its RNA. The enzyme's recognition capacity and specificity are so different from those of viral reverse transcriptases. It was wonderful to see structural evidence for that.

**PNAS:** The discovery of reverse transcriptase practically rewrote life's playbook. Such game-changing findings are vanishingly rare in biology. Serendipity aside, what prepares one for such findings?

**Baltimore:** I think it's the love of discovery. Starting in the early 1960s, I developed a tremendous fascination with viruses. I kept going deeper and deeper into the nature, variety, and ways of viruses. By the time I discovered reverse transcription, I was prepared for viruses to do almost anything. In my mind there was no barrier to thinking about reversing information flow because we already knew how remarkable viruses were.

**PNAS:** Still, you reversed central dogma. How did that feel?

**Baltimore:** It felt good. There's nothing scientists like better than to discover a chink in the armor of a dogma, particularly one that has been enshrined in the field's history.

**PNAS:** You are the sole author of the publication that showcased your Nobel Prize-winning discovery. Few single-author papers get similarly wide acclaim in today's collaborative scientific climate. How do you feel about this shift in the culture of scientific publication?

**Baltimore:** There are scientific endeavors that require large groups of people to work together, like sequencing, for example. But at the heart of every great discovery are usually one or two people. They may have collaborated with others, but I believe that great discoveries come from the minds of individuals. The only counterexample I can think of is where there are really close collaborators like Watson and Crick, or Brown and Goldstein. But we treat them as one individual anyway!

Prashant Nair, *Science Writer*

1. Zhang Q, Kim NK, Feigon J (2011) Architecture of human telomerase RNA. *Proc Natl Acad Sci USA* 108: 20325–20332.

*The complete program and audio files of most presentations from this Sackler Colloquium are available on the NAS Web site at www.nasonline.org/telomerase_and_retrotransposons, including David Baltimore's presentation. Papers arising from the Colloquium are published in the companion Sackler Special Feature, "Telomerase and Retrotransposons: Reverse Transcriptases That Shaped Genomes," which can be found in this issue of PNAS. Please refer to the introduction to the Special Feature on page 20304.