

## Highlights from the Lasker Awards press conference

### Michael Grunstein

The histone proteins are extremely conserved in evolution, so between peas and cows—it's been about 2 billion years since they had a common ancestor—there are only 2 changes in 102 amino acids between these two organisms. So, they must be extremely important, but many people thought when the conservation was described, "Oh, they must be very boring!" On the contrary, we found that they're very important, not only as packing material, but as proteins that regulate gene activity.

David [Allis] started his work in an organism called tetrahymena, otherwise known as pond scum. We started with yeast. Who would have thought that these two model organisms, which are microorganisms, would be so germane to the human condition? I think that's a plug for basic research!

When we started, the study of histones was as basic as basic research could get. They were thought to be unimportant in regulating genes.

We work with yeast, which is not exactly an exciting organism, but I considered it to be a racecar when compared to other organisms at the time. There was so much enticement in using yeast genetics to study problems.

### C. David Allis

I think it's 100% clear that understanding fundamental biological problems in whatever model organism you choose is well worth the pay-off down the road of having potential clinical applications. It's great that the Lasker Foundation recognizes that important piece of science.

We were particularly possessed in trying to follow up on a hypothesis that actually was put forward about 50 years earlier here at Rockefeller University by Vince Allfrey, who had identified these chemical modifications on these histone proteins, and suggested that they might act as a switch—if you will—for gene regulation. One particular way to come at [testing this hypothesis] would be to identify the molecules—to actually purify the molecules—that might be responsible for either adding or subtracting these chemical groups in the first place. We now refer to these as "writers" if they put the marks on and "erasers" if they take the groups off.

We contributed to identifying these molecules, and almost as soon as they were identified, it was fairly clear that many of them were already important players [based on data] from other laboratories, in terms of being either gene activators in nature or gene repressors in nature. But maybe more importantly, they were already identified as being dysfunctional in various human cancers.

### Joan Steitz

When I started, RNA was just the middle molecule in the paradigm DNA makes RNA makes protein. It was just the messenger. What's happened since then—and I feel so privileged to have been a part of many of these discoveries—is that our landscape, the world of RNA, has just exploded! What we now

realize is that RNA plays a regulatory role in so many of the processes that get the information out of our genes and into the working proteins that make our cells do what they do.

The one achievement for which I think our lab is best known is the discovery of these little particles in cells that have RNA in them called snRNPs. (They also have protein.) What these little particles do is contribute to the splicing process, by which I mean that our DNA has sense regions in it and also has nonsense regions in it. Those nonsense regions need to be taken out after the DNA has been copied into RNA. These little particles, snRNPs, assemble at the ends of those nonsense regions and very precisely snip out what needs to be thrown away. Then they glue back together the ends to make what should actually be a messenger RNA for protein.

This has all been very basic research. I'm very excited and pleased about the fact that it has now made an impact on the clinic in terms of RNA therapeutics.

I did this with a wonderful lab full of younger colleagues that were enthusiastic, innovative, and insightful, and it's to them that I'm really most grateful.

John Glen

In the early days, there were some factions within the company that didn't see the commercial potential and were worried about the vehicle we were using at the time. There was one particular meeting I can recall, that by 5 votes to 4, we agreed to continue with the program; it was very nearly knocked on the head at a very early stage.

As a veterinary anesthesiologist, I was using the drugs for anesthesia that were available at the time and I developed a research interest in looking at the new drugs that were being introduced in human medicine. I could see where there was opportunity for potential improvement on the drugs that we had.

What we were required to do was to use animal models to test chemical compounds and to look at a large number of compounds to see if we could find something that would have the profile we were looking for.