



After the Fact | [Scientists at Work: Craig Mello on the Mysteries of Genetic Code](#)

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TRANSCRIPT

Award presenter: Professor Fire, Professor Mello. Your discovery of RNA interference has unraveled a new principle for regulating the flow of genetic information. It has added a new dimension to our understanding of life and provided new tools for medicine. On behalf of the Nobel Assembly at Karolinska Institutet, I wish to convey to you our warmest congratulations, and I ask you to step forward to receive the Nobel Prize from the hands of his majesty, the king.

[Music, applause]

Dan LeDuc, host: That's the 2006 awards ceremony for the Nobel Prizes. Researchers Andrew Fire and Craig Mello received the prize in physiology or medicine. Today we're talking with Craig Mello about their remarkable discovery—and what it means for the future of medicine.

[Music]

Dan LeDuc: From The Pew Charitable Trusts, this is "After the Fact." I'm Dan LeDuc.

Science teaches us about our world and ourselves. In this installment of our "Scientists at Work" series, we're looking inward, inside the very cells that make up who we are.

Our data point is four. Just four letters in the DNA alphabet make up you, me, and every living thing on the planet.

In 1998, Craig Mello and his colleague Andrew Fire published a paper in the journal *Nature* detailing a dramatic discovery relating to DNA. It involves something called RNA interference. It often takes many years for the potential of a discovery to be realized and earn a Nobel Prize. For this pair of researchers, it took less than a decade to achieve one of science's greatest honors.

Dr. Mello was a Pew biomedical scholar, and he continues to chair the advisory committee for the program for young researchers. He's going to explain the findings



that led to the Nobel Prize in a bit, but first we'll talk about his enthusiasm and total love for science and discovery.

Craig Mello, Pew biomedical scholar and Nobel Prize winner: The thing that got me interested in science—when I was a kid, I was reading *The Washington Post* as a high school student. And I read that the human insulin gene had been cloned into bacteria and that bacteria could read the human genetic code and make insulin for patients. And I thought to myself, “That is powerful.”

Dan LeDuc: You bet.

Craig Mello: You know, “How can that be?” Because my dad is a paleontologist working at the Smithsonian, and I knew that life is ancient. How can the genetic code still be the same after billions of years of evolution, evolutionary time? And so I got fascinated by that, by molecular genetics, I guess we'd call it now. By DNA.

How does DNA work? How does information get passed from one generation to the next? And so I was looking for an organism to study that. How does information pass, and how is information handled by cells? And it's really hard to study that in a human, because, you know, obviously for ethical reasons, and so on, you can't dissect or do whatever.

Dan LeDuc: Sure. Right, right.

Craig Mello: And realizing that this genetic mechanism was so ancient that it was even shared between yeast and bacteria and humans, I chose to work as a graduate student on this little microscopic worm called the nematode *C. elegans*.

And these animals are very much like us in that they have a nervous system, muscles, intestine.

Dan LeDuc: How big are they?

Craig Mello: They're about the size of a comma on the printed page.

Dan LeDuc: Wow.

Craig Mello: So you need a microscope to see them. But they're transparent.

Dan LeDuc: But they have all of these things like us, and yet they're that size?



Craig Mello: Yeah. You know how small they are? You cannot be a smaller animal than these animals are. They have about 1,000 cells. In their intestine they have one cell that's a doughnut. And that—what it is, it's a cell that encloses the lumen of the gut; actually of the pharynx, where the mouth is—and that cell circles around, migrates around the lumen, and makes this doughnut-shaped cell that has a musculature in it and can function like a little muscle in the mouth of the animal.

So they're really tiny. And importantly for my interest in genetics and genomics, and this mechanism of inheritance, they reproduce incredibly prolifically. They produce 300 progeny in three days.

Dan LeDuc: Wow.

Craig Mello: They could—

Dan LeDuc: You have plenty of worms to work on.

Craig Mello: Yeah. And they eat bacteria. So you can grow millions of them in the laboratory, and you can put them through hundreds of generations in a year. So it's a very, very convenient system in which to study genetic inheritance. And so I started working on the animal. And no one had ever introduced DNA back into an animal before.

Both Andy and I independently started working on how to introduce DNA back into this animal. And that's how we got to know each other. So the backdrop is that these two guys who thought it was important to work on worms—

Dan LeDuc: Right, right.

Craig Mello: *[Laughing]* We're studying these animals, trying to figure out these really ancient mechanisms of inheritance, how its DNA information passed on, and there was something really fundamental that we didn't understand. To me, it just seemed absolutely amazing that information could remain so—you know, instead of telephone tag, where the information deteriorates—

Dan LeDuc: Right.

Craig Mello: You know that game where you pass a message along and by the time it's gone through four or five rounds, it's totally unrecognizable. Life does a hugely better job of that. *[Laughs]*

Dan LeDuc: *[Laughing]* Thank goodness, right?



Craig Mello: I mean, an incredibly better job. So anyway, so there was this feeling—and I always try to tell people that you've got to—it's sort of you've got to believe, in a way, you've got to believe there's an answer.

Dan LeDuc: Right, right.

Craig Mello: Or you wouldn't be a scientist. You wouldn't be out there looking if you didn't think there was something exciting to find.

Dan LeDuc: If you didn't think there was something to look for. Yeah.

Craig Mello: Right? So we were definitely looking for something. But when we found this incredibly surprising phenomenon, it was not what we were looking for. This, like, blew our socks off.

Dan LeDuc: So help people understand what it is. Because I could try to say it, and I'll get it wrong.

[Laughter]

Craig Mello: So what we discovered was that when you introduced nucleic acids in the form of RNA—now, usually when I give a seminar to a lay audience, I give them a long lecture about what RNA is.

Dan LeDuc: Okay.

Craig Mello: So everybody knows about DNA and the beautiful double helix, right? You can just look at that double helix and you can see how information is stored in there. And the steps in the staircase of that helical DNA are base pairs, we call them.

Base pairings are incredibly sequence-specific pairings. And the genetic code is really, really simple, actually. It's just—there's only four letters in the genetic code.

Dan LeDuc: And that's our data point for this episode, those four letters. Tell us what they do.

Craig Mello: They are used to form words, essentially. We call them words or codons, that specify the amino acids that are assembled into protein chains to make our functional proteins in the cell.



So the genetic code is relatively simple and straightforward. And you have what's called a messenger RNA. So the DNA has the primary sort of stored information. And the messenger RNA is sort of a dynamic form of the same information. It's a copy that goes out and encounters the machinery that translates that information into proteins.

And we were putting RNA into this animal *C. elegans*. And we were using this microinjection procedure where we would insert the needle into the germ line of the animal. The germ line is the cell lineage that produces the eggs and the sperm.

We figured out how to introduce DNA into the germ line so that we could get progeny that have the DNA that we added back to the animal. It's sort of like gene therapy for worms. If they're missing a gene, we can put it back.

Dan LeDuc: Right, put it back, right.

Craig Mello: We began to notice incredibly, incredibly odd things. For example, we put a piece of RNA in that—it looks just like an mRNA piece, a piece of an mRNA. And instead of getting any kind of activity, the corresponding gene that matched the genetic information that we were adding would turn off.

Dan LeDuc: Hmm.

Craig Mello: Okay?

Dan LeDuc: And that's new. That is like, holy cow.

Craig Mello: Wholly unexpected. Extremely odd. Not only that, RNA is much less stable than DNA, typically. For example, in serum or cell lysates, there are lots of enzymes that will rapidly degrade RNA. So usually RNA has a very short lifetime. However, we discovered that when we injected the RNA anywhere into this animal, the silencing signal that I just told you was very surprising would spread throughout the body of the animal into all the tissues.

So there was a systemic movement of a sequence-specific silencing that would precisely inactivate the gene that corresponded in its arrangement of those—you know, the genetic information. That same gene would get turned off in all the cells throughout the body. So the silencing signal was moving systemically.



So we were totally scratching our heads over how this could even be true. It was really very surprising. So in a way, no eureka. Because I think eureka comes from understanding, right? Not from being totally dumbfounded. *[Laughs]*

Dan LeDuc: *[Laughing]* That was like, “Look what we found,” and then you scratch your head and say, “What is it?”

[Laughter]

Craig Mello: Yeah, so it's like the opposite of eureka, right? It's like, what is going on? So yeah, we were excited by that. But we were also mystified. And as in almost every really exciting discovery, there's a lot of serendipity. So it turns out that silencing effect was incredibly potent, long-lasting, and systemic.

So the worms eat the bacteria, inadvertently ingesting double-stranded RNA that the bacteria make that are specifically targeting an essential gene in the worm. And because the worm has this RNA interference mechanism, it recognizes that double-stranded RNA, and it silences its own gene. So we're kind of tricking this antiviral system that the animal had into silencing its own gene. These animals only live a short time, but the silencing could be passed to their offspring.

Dan LeDuc: Oh wow.

Craig Mello: And their offspring could transmit the silencing to their offspring. So we were seeing days and even weeks of silencing. We've since shown that in fact, in some cases, you can have a gene that becomes very stably silenced and you can propagate it, maybe indefinitely.

So this kind of silencing was something entirely new. And we were looking—to a large extent we're still looking—to try to understand the mechanism. But we did uncover a really interesting feature of a type of trigger for this kind of silencing. And we discovered it again, more or less by chance.

It turns out that when we were injecting this RNA, we would make it in the laboratory using enzymes that are to some extent a little bit overactive. And what those enzymes will do is they'll make the strand that you intended to make, but then because of their sort of inherent activity, they'll actually go back and copy the other strand again, and they'll make both strands of the RNA.

And RNA, like DNA, can fold up into these helical structures. Now, viruses often have genomes made out of RNA. And so Andy got the idea that maybe these enzymes were



making a little bit of double-stranded RNA. And that was what was triggering this reaction. Maybe this is an immune reaction, was the idea.

And so we tested that idea. And it was absolutely clear that when we made double-stranded RNA intentionally, instead of single-stranded RNA, that matched a gene, would turn off the gene.

So that was 1998. We published the paper saying, “There's this incredibly weird response to double-stranded RNA. You put double-stranded RNA into the animal and it will find matching information and turn it off.” That was totally unexpected. And, moreover, our paper had no explanation for it.

[Music]

Dan LeDuc: Discovery is exciting. Knowledge is important. But then the role of scientists is also to help apply that. What will be the outcomes for society from your discoveries?

Craig Mello: It's really actually very exciting. We expect to see approval of the first RNA interference drug.

Dan LeDuc: And help people understand how that would work and what it actually means?

Craig Mello: What it means is that you would have an injectable therapy. In the case of the drug likely to be approved, it's a subcutaneous injection into the fat. And it targets a gene in the liver that's involved in or important in the genetic disorder that leads to hypercholesterolemia and invariable, you know, lethality—it's a terrible genetic disease.

This treatment looks like it has a strong disease-modifying effect. In other words, it slows progression dramatically in these patients. It may even stop it. So it's very exciting.

Dan LeDuc: As a researcher yourself, these next steps that you're describing, that have occurred with your discovery over the last two decades, are those things that you feel compelled to pursue yourself? Or do you feel like, “Hey, I did my part and I've got other interests?” And now clearly there's a lot of people interested in your discovery and want to run with it.

Craig Mello: Well, I—for full disclosure, I should say that I am actively involved in trying to help move this along into a clinic.

Dan LeDuc: Sure.



Craig Mello: Not only does it interest me, but I feel passionately about that. Remember, when I was reading *The Washington Post*, I thought, “This could help people.”

Dan LeDuc: Right.

Craig Mello: I think there's a lot of scientists who do it because it's interesting and piques their curiosity. But I think somewhere in the back of their mind, they know they're not just filling out a crossword puzzle.

Dan LeDuc: Right.

Craig Mello: You know, that this might actually make a real difference in a patient's life.

Dan LeDuc: So, doctor, when you talk to the public, what do you like them to know about science?

Craig Mello: I think that science is driven by beauty, just the same way art is. There's beauty in nature. And we, I think, as scientists and as just as human beings—because I think all humans are scientists at heart—when you see something beautiful, it's not that you want to dissect it. There's this sense of awe about it.

You get curious and you just try to understand what you're seeing a little better. And what always happens is it gets more mysterious, not less.

[Music]

Dan LeDuc: Well, Craig Mello, thank you so much for the time today and for all you've done.

Craig Mello: Well, thank you. It's been a pleasure.

Dan LeDuc: In August, the FDA approved the first drug based on Craig Mello's research. It will treat nerve damage caused by a rare genetic disorder that also causes heart and digestive disease and can be fatal. Other drugs are in the works.

You can read more from him—including an essay on why he believes science transcends borders and can unite people everywhere—at our website, pewtrusts.org/afterthefact.

Our thanks to Nobel Media for audio from the awards ceremony.

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Thanks for joining us. For The Pew Charitable Trusts, I'm Dan LeDuc, and this is "After the Fact."

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