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RESEARCH NEWS

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HHMI Investigator Craig C. Mello Wins 2006 Nobel Prize in Physiology or Medicine

The Nobel Assembly at the Karolinska Institute announced this morning that the 2006 Nobel Prize in Physiology or Medicine was awarded to Craig C. Mello, a Howard Hughes Medical Institute investigator at the University of Massachusetts Medical School, and Andrew Z. Fire at Stanford University School of Medicine. The two were honored for their discovery of RNA interference - gene-silencing by double-stranded RNA.

According to a news release issued by the Karolinska Institute, Mello and Fire were honored for discovering "a fundamental mechanism for controlling the flow of genetic information. In 1998, the American scientists Andrew Fire and Craig Mello published their discovery of a mechanism that can degrade mRNA from a specific gene. This mechanism, RNA interference, is activated when RNA molecules occur as double-stranded pairs in the cell. Double-stranded RNA activates biochemical machinery which degrades those mRNA molecules that carry a genetic code identical to that of the double-stranded RNA. When such mRNA molecules disappear, the corresponding gene is silenced and no protein of the encoded type is made."

For decades, RNA molecules have been regarded as little more than DNA's messengers, ferrying the genetic code to the cell's protein-building factories. Craig Mello's research has helped to establish that certain RNA molecules play a far more impressive role in the cell. In a groundbreaking discovery, he found that short snippets of RNA could silence the expression of targeted genes. This phenomenon, called RNA interference, not only has become an indispensable means for studying gene function but has been found to be a normal part of gene regulation during embryonic development and may play a role in cancer and other diseases.

Digging for dinosaur bones lured Mello into science. Mello's father, a paleontologist with the Smithsonian Institution, frequently took his son on fossil-hunting expeditions in the western U.S. "Even as a kid, I was captivated by the concept of deep time, the history of the Earth and the origins of human life," he said. As a high school student in the late 1970s, Mello's fascination turned to genetic engineering. Scientists had just cloned the human insulin gene and inserted its DNA into bacteria, which by multiplying over and over again could produce a limitless supply of synthetic insulin. This achievement dramatically changed the outlook for millions of diabetics worldwide, who had been relying on insulin from pigs and cows to stay alive. "The idea that research could have a real impact on human health really intrigued me," he recalled. "And that was something that had been missing for me in the field of evolutionary biology."

When Mello started his own laboratory at the University of Massachusetts Medical School, he turned his attention to developing a more effective way of blocking the expression of specific genes in the developing embryo as a way to study their function. Working with *C. elegans* embryos, he injected RNA into the worms and was surprised to find that the interference effect was far more robust than expected. The RNA interference spread from cell to cell throughout the worm's body, regardless of the site of injection, and was transmitted from one generation to the next. "This was unheard of," Mello explained. "Something extremely interesting was going on but we didn't know what it was." After further studies conducted in collaboration with Andrew Fire of the Carnegie Institution of Washington, the pair revealed in a paper published in *Nature* in 1998 that the gene-silencing effect was in fact caused by double-stranded RNA.

Since their discovery, RNA interference has been shown to silence genes in organisms ranging from plants and fruit flies to humans. It works by duping the cell into destroying the gene's messenger RNA before it can produce a protein. Scientists have speculated that the mechanism developed hundreds of millions of years ago as a way to protect organisms against invading viruses, which sometimes create double-stranded RNA when they replicate. Today, RNA interference has become the state-of-the art method by which scientists thwart the expression of specific genes to determine their function.

Before RNA interference came to light, Mello studied the mechanisms cells use to differentiate and communicate during the earliest stages of the embryogenesis, a focus that continues in his laboratory today. His research has demonstrated that a cell's position in the embryo can determine what type of tissue it will ultimately become, and he has identified numerous genes involved in determining cell fate in *C. elegans* embryos. Mello's laboratory is now evenly divided between projects investigating RNA interference and embryonic development, and the two fields continue to converge. "It really is the most amazing feeling when you first see the connections long before you can prove they exist," Mello noted.