Victor Ambros receives 2015 Breakthrough Prize for co-discovery of microRNAs

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Victor R. Ambros, PhD, professor of molecular medicine at the University of Massachusetts Medical School, has been awarded a 2015 Breakthrough Prize in Life Sciences for his co-discovery of a new world of genetic regulation by microRNAs, a class of tiny RNA molecules that inhibit translation or destabilize complementary mRNA targets. Honored with his long-time collaborator Gary Ruvkun, PhD, professor of genetics at Massachusetts General Hospital and Harvard Medical School, Dr. Ambros, the Silverman Chair in Natural Sciences and co-director of the RNA Therapeutics Institute, was one of six biomedical researchers honored, each of whom received a $3 million prize. In total, the Breakthrough Prizes awarded more than $36 million this year.

Established in 2013, the Breakthrough Prizes are bestowed in the fields of life sciences, physics and mathematics to celebrate scientists and generate excitement about the pursuit of science as a career. Founded by technology and Internet entrepreneurs Sergey Brin and Anne Wojcicki, Jack Ma and Cathy Zhang, Yuri and Julia Milner, and Mark Zuckerberg and Priscilla Chan, the prizes are funded by grants from the Brin Wojcicki Foundation; Mark Zuckerberg's fund at the Silicon Valley Community Foundation; the Jack Ma Foundation; and the Milner Foundation. Laureates of all prizes are chosen by selection committees which comprise prior recipients of the prizes.

"This year's life sciences laureates have made some spectacular discoveries, from a new kind of gene to a Parkinson's treatment that has improved the lives of many," said Wojcicki, co-founder and chief executive officer of the personal genomics company 23andMe. "It's energizing to be in the company of such brilliant and fertile minds."

The awards were presented at an exclusive gala co-hosted by Breakthrough Prize co-founders and Vanity Fair editor Graydon Carter at NASA's Ames Research Center. Hollywood personality Seth MacFarlane was master of ceremonies for the 2nd Annual Breakthrough Prize Ceremony, which also featured actors Kate Beckinsale, Benedict Cumberbatch, Cameron Diaz, Jon Hamm and Eddie Redmayne as presenters.

"The world faces many fundamental challenges today, and there are many amazing scientists, researchers and engineers helping us solve them," said Zuckerberg, founder and CEO of Facebook. "This year's Breakthrough Prize winners have made discoveries that will help cure disease and move the world forward. They deserve to be recognized as heroes."

The ceremony was produced and directed by Emmy Award-winning Don Mischer Productions and will be simulcast in the United States on Discovery Channel and Science Channel on Nov. 15 at 6 p.m. and televised globally the weekend of Nov. 22 on BBC World News.

Regulation by microRNA

The unlikely discovery of microRNAs, also known as miRNA, and their function dates back to the 1980s when Ambros and Dr. Ruvkun were postdoctoral fellows at MIT, studying how the lin-4 and lin-14 genes regulate developmental timing in the nematode C. elegans. Ambros and Ruvkun wanted to understand how mutations of the lin-4 kept the worm's larvae from developing into fully formed animals, while mutations in the lin-14 gene caused the larvae to mature prematurely.

In 1989 Ambros established that lin-4 acts as a repressor of lin-14 activity. How lin-4 achieved this repression, however, was not known. In 1991, it was Ruvkun who established that genetic anomalies in lin-14's sequence—specifically in an area of the gene called the 3' untranslated region (3' UTR)—were associated with excess production of the lin-14 protein produced from the messenger RNA that lin-4 targets.

A year later, Ambros successfully isolated and cloned lin-4. To his surprise, Ambros found that the gene's product was not a standard regulatory protein as he had expected, but a tiny non-protein-coding strand of RNA about 22 nucleotides long that is conserved in other nematode species.

Working together, Ambros and Ruvkun compared the lin-4 and lin-14 sequences and discovered that the 22-nucleotide lin-4 RNA and the 3' UTR were partially complementary and that the short complementary regions were highly conserved in evolutionary comparisons to other nematode lin-4 and lin-14 genes. They hypothesized that lin-4 RNA regulated lin-14 by binding to its 3' UTR sequences. Ruvkun then showed that lin-4 controlled the translation of the lin-14 mRNA into protein and it was through this channel that lin-4 achieved repression of lin-14.

Ambros and Ruvkun published back-to-back studies in Cell in 1993 that described these remarkable findings. The discovery, however, seemed more an oddity than a breakthrough at the time, in part because the lin-4 gene existed only in the worm.

The broader importance of the findings—the idea that miRNAs might play a role in gene expression in other organisms—was not immediately clear. Then, in 1999, British plant biologist David Baulcombe, PhD, professor of botany at the University of Cambridge, reported on his own groundbreaking discovery that a similar class of RNAs is involved in a related silencing process affecting viruses, transposable elements and gene expression in plants. This was followed the next year by Ruvkun's twin discoveries that he had found a second microRNA—let-7—in C. elegans and that let-7 was evolutionarily conserved across the animal kingdom, including in humans. The results showed that the activity of microRNAs was not just restricted to a single species of worm.

Since this discovery, researchers have identified almost 2,000 unique human miRNAs that are responsible for regulating more than half of all human genes. Study of these and other related classes of small RNAs has exploded into an exciting new field of research. Scientists have linked the gene-silencing abilities of these tiny molecules to a diverse range of important developmental and physiological processes in both plants and animals. miRNAs have now been implicated in a wide range of both normal and pathological activities including embryonic development, blood-cell specialization, muscle function, heart disease and viral infections.

Ambros completed his undergraduate and graduate degrees, as well as his postdoctoral research, at the Massachusetts Institute of Technology. After completing his postdoctoral fellowship, Ambros joined the faculty at Harvard University in 1984 and remained there until 1992, when he accepted a faculty position at Dartmouth College. He arrived at UMass Medical School in 2007. Ambros has maintained a very close collaborative relationship with Ruvkun through the years, though the two have not worked in the same laboratory since the early 1980s.

At UMMS, Ambros continues his research on microRNA function and gene regulation during development, and is focused on understanding the genetic and molecular mechanisms that control cell division, differentiation and morphogenesis in animals.

Provided by University of Massachusetts Medical School