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Ambros, Baulcombe, and Ruvkun Share $500,000 Gruber Genetics Prize for Pioneering Discoveries of microRNAs and small interfering RNAs, and their Key Role in Gene Expression

Victor Ambros

David Baulcombe

Gary Ruvkun

June 17, 2014, New Haven, CT – The 2014 Gruber Genetics Prize will be awarded to Victor Ambros, PhD, professor of molecular medicine at the University of Massachusetts Medical School; David Baulcombe, PhD, professor of botany at the University of Cambridge; and Gary Ruvkun, PhD., professor of genetics at Massachusetts General Hospital and Harvard Medical School. These three distinguished scientists are being recognized with this prestigious international prize for their pioneering discoveries of the existence and function of microRNAs and small interfering RNAs, molecules that are now known to play a critical role in gene expression.

The award will be presented to the recipients in San Diego, CA on Oct. 19 at the annual meeting of the American Society of Human Genetics.

“The discoveries of these three pioneering scientists have opened major new areas in chemistry, biology, agriculture and medicine and have revealed fundamental mechanisms that are shared among organisms as diverse as plants and animals, including humans,” said Robert Horvitz, Gruber and Nobel Prize laureate, and David H. Koch Professor at MIT.

The road to the discovery of microRNAs and their function began in the 1980s, when Ambros and Ruvkun were postdoctoral fellows in the lab of (future Gruber and Nobel laureate) H. Robert Horvitz, PhD, at the Massachusetts Institutes of Technology (MIT), studying the *lin-4* and *lin-14* genes that regulate developmental timing in the nematode *Caenorhabditis elegans.* Mutation of *lin-4* kept the worm’s larvae from developing into fully formed animals, while mutations in another gene, *lin-14,* caused the larvae to mature prematurely. Ambros and Ruvkun collaborated on the isolation of the *lin-14* gene.

In 1989, Ambros, in his own lab at Harvard, established that *lin-4* acts as a repressor of *lin-14* activity, although the molecular mechanism for that repression awaited further investigation. In 1991, Ruvkun and his colleagues in his Harvard lab 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 and his colleagues successfully isolated and cloned *lin-4.* To his surprise, Ambros also found that the gene's product was not a standard regulatory protein, but a tiny non-protein-coding strand of RNA about 22 nucleotides long that is conserved in other nematode species, showing a selection on its RNA sequence. Around the same time, Ruvkun demonstrated that particular elements of the *lin-14* 3' UTR are conserved in other nematodes, suggesting evolutionary selection on their function. 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 regions of complementarity 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 the repression mediated by *lin-4* was via control of the translation of the *lin-14* mRNA into protein.

The two scientists published back-to-back studies in Cell in 1993 that described these remarkable findings. But the broader importance of the findings—the idea that the small RNAs (later dubbed microRNAs) might play a role in gene expression beyond *C. elegans*—was not immediately clear. Then, in 1999, British plant biologist David Baulcombe 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.

In the ensuing years, the 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 process in both plants and animals.

"At one time, these small RNAs were considered just an unimportant scientific oddity," says Huda Zoghbi, chair of the Selection Advisory Board to the Prize. "But thanks to the exciting work of Victor Ambros, Gary Ruvkun, and David Baulcombe, we now know that they are anything but unimportant, both to human health and to the health of the planet."

Additional Information

In addition to the cash award, each recipient will receive a gold laureate pin and a citation that reads:

The Gruber Foundation proudly presents the 2014 Genetics Prize to Victor Ambros, David Baulcombe, and Gary Ruvkun for the discovery of small non-coding RNAs and for the demonstration of their central roles in the regulation of development and gene expression.

This research, which combined elegant genetics and molecular biology, demonstrated that a previously unknown class of RNAs (called microRNAs and small interfering RNAs) affected post transcriptional gene activity in nematodes and vertebrates (Ambros and Ruvkun) and in plants (Baulcombe). Their seminal findings led to an explosion in research that greatly increased our understanding of the control of such diverse processes as cell differentiation, developmental timing, cellular metabolism, cell death, and pathologies such as viral infection and cancer.

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Laureates of the Gruber Genetics Prize:

- **2013: Svante Pääbo,** for pioneering the analysis of ancient DNA
- **2012: Douglas C. Wallace,** for his groundbreaking contributions to mitochondrial genetics
- **2011: Ronald Davis,** for his pioneering development and application of recombinant-DNA techniques
- **2010: Gerald Fink,** whose work in yeast genetics advanced the field of molecular genetics
- **2009: Janet Davison Rowley,** for her seminal discoveries in molecular oncology
- **2008: Allan C. Spradling,** for his work on fly genomics
- **2007: Maynard V. Olson,** for his contributions to genome science
- **2006: Elizabeth H. Blackburn,** for her studies of telomeres and telomerase, and her science advocacy
- **2005: Robert H. Waterston,** for his pivotal role in the Human Genome Project
- **2004: Mary-Claire King,** for three major findings in modern genetics: the similarity of the human and chimpanzee genomes, finding a gene that predisposes to breast cancer, and forensic genetics.
- **2003: David Botstein,** a driving force in modern genetics who established the ground rules for human genetic mapping
- **2002: H. Robert Horvitz,** who defined genetic pathways responsible for programmed cell death
- **2001: Rudolf Jaenisch,** who created the first transgenic mouse to study human disease

The Prize recipients are chosen by the Genetics Selection Advisory Board. Its members are: **Bonnie Bassler,** Princeton University; **Martin Chalfie,** Columbia University; **Helen Hobbs**, University of Texas Southwestern; **Richard Lifton,** Yale School of Medicine; **Maynard Olson,** Genome Center, University of Washington; **Allan C. Spradling,** Carnegie Institution, Howard Hughes Medical Institute; and **Huda Zoghbi,** Baylor College of Medicine (Chair).

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By agreement made in the spring of 2011 The Gruber Foundation has now been established at Yale University.

The Gruber International Prize Program honors individuals in the fields of Cosmology, Genetics and Neuroscience, whose groundbreaking work provides new models that inspire and enable fundamental shifts in knowledge and culture. The Selection Advisory Boards choose individuals whose contributions in their respective fields advance our knowledge and potentially have a profound impact on our lives.

The Genetics Prize is presented to a leading scientist, or up to three, in recognition of groundbreaking contributions to any realm of genetics research.

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For more information on the Gruber Prizes, visit www.gruber.yale.edu, e-mail info@gruber.yale.edu or contact A. Sarah Hreha at +1 (203) 432-6231. By mail: The Gruber Foundation, Yale University, Office of Development, PO Box 2038, New Haven, CT 06521.

Media materials and additional background information on the Gruber Prizes can be found at our online newsroom: www.gruber.yale.edu/news-media