Scientists explore a lot of dead ends, and Victor Ambros’ instincts told him that he’d arrived at another. His Dartmouth lab had found a gene in C. elegans, a tiny worm, that did not produce the regulatory protein the team had expected. It produced a single strand of RNA only 22 nucleotides long. This was in the early 1990s, and nothing like it had been seen before. The little RNA was interesting, but Ambros suspected it was a curiosity that existed only in worms. He remained a skeptic until 2000, when another lab published a paper which showed that a second example of this microRNA, as it came to be called (miRNA), was conserved across a wide range of living things—from plants to nematodes to sea urchins to humans. Ambros says that after he read that paper, he stared out his window for 10 minutes, reorganizing his view of the universe.

Since then, scientists have sequenced many thousands of examples of miRNA. They’ve learned that they function as gene silencers—regulating the expression of genes critical to normal development and biological function—and occasionally as gene activators. Viruses manipulate their hosts by targeting miRNA pathways, and dysfunction of miRNA activity leads to some cancers (in which case they act as oncogenes); but happily, in some cases, miRNAs act as tumor suppressor genes. For his work, Victor Ambros won the Lasker Basic Medical Research Award in 2008 and during our recent, annual Science Festival, our own 2009 Dickson Prize in Medicine.

Three years ago, here at the medical school, Bino John and collaborators accidentally discovered RNA even smaller than micro. It was a perfect example of chance favoring the prepared mind. His lab was probing a 23-nucleotides-long miRNA from the Kaposi’s sarcoma herpes virus. Bino had refined the northern blot technique to make it more sensitive, and the group unexpectedly detected RNA that was only 17 nucleotides long. They were then able to sequence a great number of what Bino dubbed usRNAs (unusually small RNAs) from a wide variety of tissues. Bino was stunned to find that usRNAs appeared to outnumber miRNAs in their samples. Much like miRNA, one of the functions of usRNA seems to be silencing specific genes.

We are only beginning to understand the importance of usRNA, but, as with miRNA, we can bet that this finding will not lead to a dead end. Several companies are aggressively working to develop small molecules that act on miRNAs—to inhibit or activate their role in diseases such as cancer. All based on a chance observation in an “elegant” worm! What better rationale for the pursuit of basic science?

Everything in biology is in equipoise: Our cells synthesize proteins and degrade them. We produce genetic instructions when needed and silence them with miRNA and usRNA when they are not. The English author and mystic James Rhoades once wrote:

*It is the joy of joys, / To thrill co-operant with the primal cause / Of the unswerving laws / Which hold in everlasting equipoise / Those balances of God, / The visible and invisible Universe.*

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