

## [HOW RNA INTERFERENCE WORKS]

Often hailed as the most powerful new biochemical tool in decades, RNA interference was first demonstrated in animals in the *C. elegans* worm in 1998 and is now cited in thousands of scientific papers. The process selectively disables gene expression by attacking the messenger RNA created by a specific gene — without destroying the gene itself. RNAi naturally occurs in a wide range of organisms, and its roles are studied by Whitehead Member David Bartel and many other investigators (see next page).

RNAi begins with double-stranded RNA, which is sliced into short interfering RNAs (siRNAs). Integrated into RNA-inducing silencing

complexes (RISCs), the siRNAs then attach to complementary messenger RNA molecules and break them.

This pathway doesn't work in mammals, whose cells are shut down by the introduction of the double-stranded RNA. But in 2001, Thomas Tuschl, who earlier had worked as a postdoc in the Bartel lab, announced an RNAi variant that overcomes this barrier by slipping synthetic siRNAs into mammalian cells. Labs worldwide now have developed a number of approaches to exploit RNAi in mammals, and are furiously investigating potential research and medical applications.

### [RNAi in plants and animals]

**1** Long double-stranded RNAs are introduced to the organism.

**2** The double-stranded RNAs are chopped into short interfering RNAs (siRNAs) by an enzyme called Dicer.

**3** The siRNAs are assembled into RNA-inducing silencing complexes (RISCs), unwinding as they do so.

**4** The unwound siRNA strands guide the RISCs to complementary messenger RNA molecules. They attach to and then break the messenger RNA, silencing gene expression.

### [RNAi in mammals]

**1** Short interfering RNAs (siRNAs) are generated by various techniques. In one technique, DNA is inserted into a DNA vector molecule and transferred into the cell, where it expresses short hairpin RNA.

**2** The short hairpin RNA is then chopped into siRNAs.

SOURCES: LABORATORIES OF DAVID BARTEL AND MICHAEL MCMANNIS, NATURE REVIEWS GENETICS AND INVITROGEN GRAPHIC: CHRISTINA ULLMAN

