

**Cover illustration**

In RNA silencing, one strand of a small duplex RNA (combs) enters a silencing complex (platter) that contains a catalytic Argonaute (pincers) to cleave a target RNA (cord). (Courtesy of M. Inudo and Y. Tomari. Artwork by N. Spencer)

**Editor, Nature**

Philip Campbell

**Publishing**Nick Campbell  
Claudia Banks**Insights Editor**

Lesley Anson

**Production Editor**

Davina Dadley-Moore

**Senior Art Editor**

Martin Harrison

**Art Editor**

Nik Spencer

**Sponsorship**Amélie Pequignot  
Reya Silao**Production**

Jocelyn Hilton

**Marketing**Elena Woodstock  
Emily Elkins**Editorial Assistant**

Alison McGill

**The Macmillan Building**

4 Crinan Street

London N1 9XW, UK

Tel: +44 (0) 20 7833 4000

e-mail: nature@nature.com



nature publishing group

# RNA SILENCING

**W**hen *Nature* published the first Insight on RNA interference (RNAi), in September 2004, it was clear that RNAi was going to have a broad impact on biology, even though only six years had passed since the seminal paper by Andrew Fire, Craig Mello and colleagues was published.

But who would have imagined how far we would come in the next four years in terms of understanding and exploiting this fundamental system of gene regulation? There is now a much clearer picture of how the small non-coding RNAs involved in this type of regulation are generated, drawn from the static images provided by crystallographic studies, together with the kinetic and mechanistic details gleaned through biochemical assays. From large-scale efforts to map how gene expression is affected by just one class of these small RNAs, microRNAs, it is easy to reach the conclusion that when studying any biological process, researchers must consider how it is regulated by small RNAs. Relationships between small RNAs and development are also being uncovered almost daily. And nimble biotechnology firms have, with breathtaking speed, aggressively translated this knowledge into therapeutic candidates.

It was no surprise that the researchers who opened this Pandora's box were awarded the Nobel Prize in Physiology or Medicine in 2006. As Göran Hansson stated in his presentation speech for the award, RNAi "has added a new dimension to our understanding of life and provided new tools for medicine". However, the story is far from complete even now. With advances in sequencing technology, for example, more classes of small RNA are being identified, and their functions are likely to continue to entice and surprise us.

With these reviews, we hope to convey some of the excitement driving this rapidly evolving field forward. We are pleased to acknowledge the financial support of Alnylam Pharmaceuticals and Roche in producing this Insight. As always, *Nature* carries sole responsibility for editorial content and peer review.

Angela K. Eggleston, Senior Editor

## REVIEWS

### 396 On the road to reading the RNA-interference code

H. Siomi &amp; M. C. Siomi

### 405 A three-dimensional view of the molecular machinery of RNA interference

M. Jinek &amp; J. A. Doudna

### 413 Small RNAs in transcriptional gene silencing and genome defence

D. Moazed

### 421 Viral and cellular messenger RNA targets of viral microRNAs

B. R. Cullen

### 426 The promises and pitfalls of RNA-interference-based therapeutics

D. Castanotto &amp; J. J. Rossi

nature  
insight