

# BIOTECH 101

## RNAi understanding the process

Much like turning off a light switch, RNA interference (RNAi) offers the ability to selectively silence or “turn off” the activity of a single gene. This technology has the potential to revolutionize our understanding of how genes work and offers new promise in therapy and treatment.

Illustration: Tavis Coburn



The 2006 Nobel Prize in Physiology or Medicine was awarded to Drs. Andrew Fire (Stanford University) and Craig Mello (University of Massachusetts Medical School) for revealing the process of RNA interference, also known as RNAi. This discovery has ushered in a new understanding of how the activity of genes can be controlled. Cited as the “Breakthrough of the Year” in 2002 by Science magazine, RNAi has generated a flurry of research, leading to several potentially promising therapies for human disease.

### The Background

**Genes**, specific segments of a cell’s DNA, serve as instructions telling cells how to make individual proteins.

**Proteins** are the key building blocks of the body, for example: collagen, which helps give our cells their shape; or hemoglobin, which allows red blood cells to carry oxygen across the body. DNA is kept safely within the confines of the cell’s nucleus, sheltered from damage and degradation. Proteins, however, are created on structures known as **ribosomes**, which are only found outside the nucleus. If the DNA is unable to leave the nucleus, how do the instructions for creating a protein reach the ribosome?

### Single- and double- RNA strands

The answer comes in the form of **messenger RNA** (mRNA), a copy of the instruction-containing part of the DNA. mRNA is created in the nucleus, but travels to the ribosome to direct the protein’s creation (see ‘The Pathway to Protein’ diagram, page 5). Among other differences, DNA is a two-stranded molecule while mRNA has only a single strand. Generally, the amount of mRNA produced for a specific gene can be correlated with the amount of protein that will be made – more mRNA usually leads to more protein.

The 1998 research by Fire and Mello noted that small double-

### RNAi - key facts

- **Proteins** are the primary building blocks of our bodies.
- **Genes** direct the production of proteins using a messenger molecule called mRNA.
- In RNA interference (RNAi), short molecules trigger the destruction of a gene’s **messenger RNA**, preventing protein from being made.
- In the lab, scientists can use RNAi to shut down protein production for a specific gene.
- The ability to selectively silence a gene has strong therapeutic potential in diseases where too much protein leads to clinical problems.

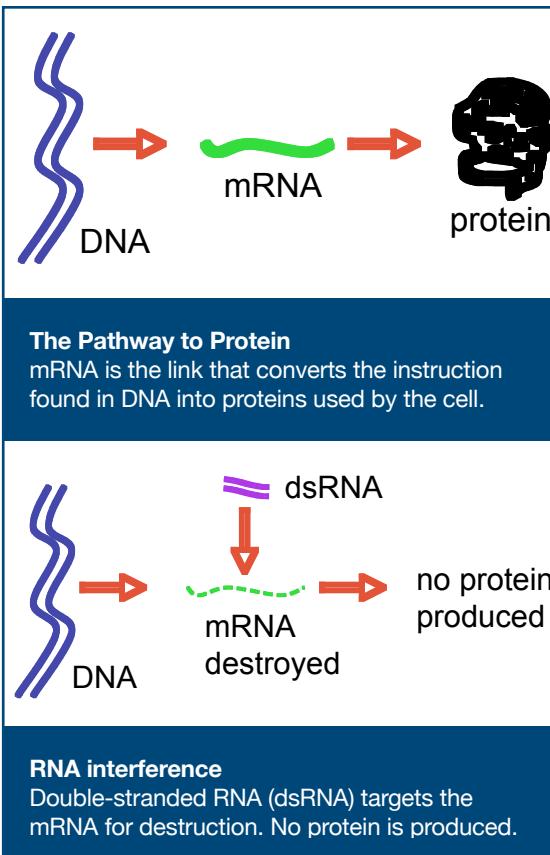
stranded RNA molecules corresponding to a specific gene could effectively stop protein production directed by that gene. The double-stranded RNA molecules coordinated the destruction of the single-stranded mRNA. In other words, the double-stranded RNA "interfered" with the mRNA, effectively silencing the activity of the gene (see 'RNA interference' diagram).

### Original role in defense

RNAi is thought to serve as a cell's natural defense against viruses, which attempt to take over a cell's protein-production mechanism by inserting their own genes into the host DNA.

Researchers have utilized the RNAi pathway to explore the effects of systematically silencing genes. Short synthetic double-stranded RNA molecules can be created in the laboratory and delivered to cells, leading to partial or complete protein shutdown.

The ability to target and deplete specific proteins has also identified RNAi as a potential therapeutic pathway. RNAi could be utilized to treat both infectious diseases and genetic disorders caused by over- or undesired production of a specific protein.



### Therapeutic Possibilities

One of the first RNAi therapies to enter clinical trials focused on a form of age-related macular degeneration, a disorder that destroys central vision.

Macular degeneration is influenced by excessive levels of VEGF, a protein that promotes blood vessel development behind the retina. These vessels can leak, leading to the vision loss. In a series of remarkable clinical trials, short fragments of double-stranded RNA that target the mRNA for VEGF were injected directly into the eyes of affected individuals.

Although intended primarily to assess safety issues, the initial trial results were promising. Two months after injection with the drug, a quarter of the patients experienced significantly clearer vision, while the

vision of the other patients had at least stabilized.

### Work in Progress

Daunting obstacles still lie ahead for RNAi therapies. These include identifying the ideal methods for delivery of RNAi molecules to the right targets, how to avoid accidental silencing of other genes and how to ensure that the drugs remain sufficiently active to provide clinical benefit.

## RNAi at HAIB

While RNAi is likely to play a key role in the research activities of HAIB investigators, it has already found a place within the Institute's associated companies. Some examples include:

**Open Biosystems** [www.openbiosystems.com](http://www.openbiosystems.com) offers gene-specific double-stranded RNA molecules to help researchers study the effects of silencing their gene of interest.

From a therapeutic approach, **Expression Genetics** [www.egencorp.com](http://www.egencorp.com) is exploring the use of RNAi in a potential delivery method for the treatment of human diseases.

## Want More Information?

Check out the following links for more about RNAi:

[www.hhmi.org/bioInteractive/rna/rnai/index.html](http://www.hhmi.org/bioInteractive/rna/rnai/index.html)

This website, hosted by the Howard Hughes Medical Institute, explains the discovery of RNAi in worms and plants.

[www.pbs.org/wgbh/nova/sciencenow/3210/02.html](http://www.pbs.org/wgbh/nova/sciencenow/3210/02.html)

From the popular PBS show NOVA, this website includes a video segment detailing the process of RNAi as well as a Q&A with Dr. Greg Hannon, a researcher at Cold Spring Harbor Laboratory and a key collaborator within the Institute.

[www.nature.com/focus/rnai/animations/index.html](http://www.nature.com/focus/rnai/animations/index.html)

This website, developed by Nature Publishing Group, features a thorough animation of the RNAi mechanism.