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## In Human Eyes, Hope Of Taming Bad Genes

### A new technique could help fight blindness or AIDS.

By ANDREW POLLACK

If all goes according to plan, about half a dozen elderly people at risk of blindness will visit Dr. Lawrence J. Singerman's retina clinic in the coming weeks to receive injections in the whites of their eyes.

The experimental injections will contain a new type of drug based on a recently discovered genetic phenomenon, called RNA interference, that has excited scientists with its versatile and powerful ability to turn off genes. The technique is now set to be tested in people for the first time.

Acuity Pharmaceuticals, a two-year-old company in Philadelphia, said recently that the United States Food and Drug Administration had granted permission for it to conduct the first human test of RNA interference — the experiment in which Dr. Singerman's clinic in Cleveland and a second clinic plan to participate. The early-stage clinical trial, largely a safety review, will test the technique against the gene that sets off the process of age-related macular degeneration, a deterioration of the retina that is the leading cause of blindness in the elderly.

Success is far from guaranteed. While RNAi, as it is known, works well in the laboratory, there are questions about whether it will work in people.

But if it does, RNAi could potentially yield a cornucopia of other drugs designed to silence errant, disease-causing genes in the body, or disarm an invading virus by knocking out its genes. A second company, Sirna Therapeutics of Boulder, Colorado, applied to the F.D.A. recently for permission to begin a trial of its own drug for macular degeneration. Several other small

biotechnology companies say they, too, are planning clinical trials in the next couple of years to use RNA interference to treat that disease and others including AIDS, hepatitis, Parkinson's and Lou Gehrig's disease.

"From the basic science that's been done in this area, I think the direction has great promise," said Dr. Singerman, president of Retina Associates of Cleveland.

RNA is a string of chemical units, called bases, that represent the letters of the genetic code. It serves as a messenger, carrying the recipe for a protein from the DNA in the genes to the cell's protein-making machinery. Proteins form much of the structure of a cell and carry out much of its activities. While DNA has two strands, RNA is usually single-stranded. If cells sense double-stranded RNA, they act to destroy it and any other RNA with the same sequence.

Scientists can harness this mechanism to prevent any gene in the body from being used to make a protein, effectively shutting off the gene. They synthesize a short string of double-stranded RNA that corresponds to part of the messenger RNA carrying the protein recipe. Rather than creating the protein, the cell destroys the messenger.

The RNAi approach involves taking a short stretch of RNA, the cousin of the DNA in genes, and delivering it into cells in the body. But RNA is quickly chewed up by enzymes in the blood or removed by the liver and kidneys and excreted. And even if the RNA survives, it cannot easily pass through the membranes surrounding the cells in which it is needed.

But supporters of the approach say that RNAi appears to be more potent than earlier techniques because it makes use of the cell's natural mechanism.

Some animal tests have demonstrated the technique's potential. According to a paper published in June, scientists at the F.D.A. led by Suzanne L. Epstein

used RNAi to partly protect mice from lethal flu viruses.

But the animal tests have not been numerous. And in some cases, to overcome the delivery obstacles, the RNA was injected into the mice at such high pressure and volume that some experienced temporary heart failure.

Acuity has an advantage on its closest competitors, Sirna and Alnylam, because of its simpler approach of using a plain double-stranded piece of RNA. Alnylam, based in Cambridge, Massachusetts, is also working on a treatment for Parkinson's disease.

Sirna is also pursuing a treatment for hepatitis C and has licensed the work done at the University of Iowa to treat Huntington's disease.

The Australian company Benitec is working with the City of Hope National Medical Center in Duarte, California, on plans for beginning tests next year of RNA interference as a treatment for H.I.V., the virus that causes AIDS.

Besides scientific and regulatory issues, the field is facing possible legal battles for control of patents, and also the challenge of attracting investors. Sirna's stock traded as high as \$8 last November but closed on September 13 at \$2.81. Alnylam was forced by a lukewarm market response to reduce the price of the stock offering to \$6 a share, down from the hoped-for \$10 to \$12. The stock closed on September 13 at \$5.82.

"This is a new technology and there are reasons for people to be skeptical until there's proof points out there," said Dr. John Maraganore, the chief executive of Alnylam.

Acuity, for its part, hopes the first proof points might soon be in the eyes of Dr. Singerman's beholders.

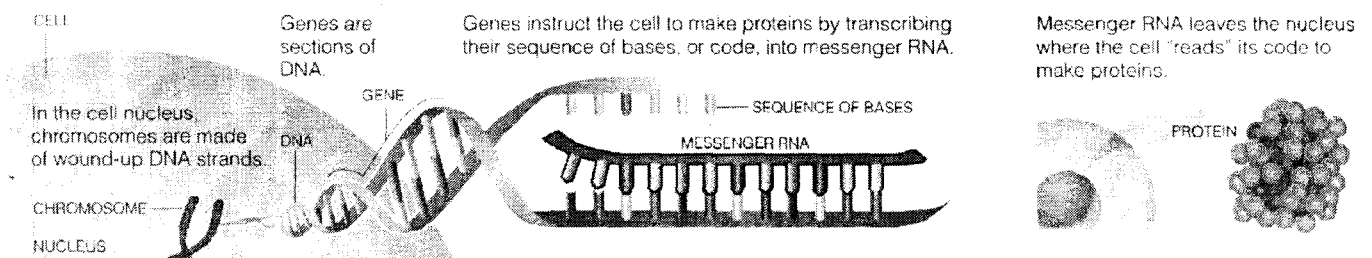




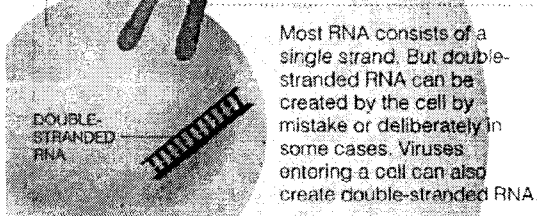
## Shutting Off Disease Genes

Medical researchers are harnessing a naturally occurring phenomenon, RNA interference, to create treatments they hope will fight disease by shutting down the genetic process that prompts a person's cells to produce disease-causing proteins.

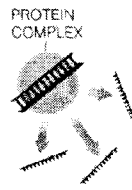
### Making a protein



### Malfunctioning messenger RNA



As a natural defense, cells create a protein complex to destroy double-stranded RNA and any matching RNA before a protein can be made.



### Using the cell's natural defense mechanism

Scientists can manufacture double-stranded versions of RNA whose code corresponds to part of the single-stranded versions that cause disease.

In theory, injecting this double-stranded RNA into a cell causes the cell to destroy it and anything with a corresponding code sequence, effectively shutting off the production of the protein.