

# Delivering on RNA's Medical Promise

**RNA-based therapies could treat everything from cancer to AIDS. New research could be removing the biggest barrier to their practical application: getting the drugs into the body.**

By Erika Jonietz  
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A new class of drugs with the potential to revolutionize the treatment of diseases ranging from cancer and Huntington's disease to influenza has moved a step closer to the clinic, as research reported in the past few weeks signals the removal of the most significant barrier to their use in humans.

In the new studies, researchers have demonstrated methods to effectively deliver treatments based on RNA interference, or RNAi—a natural process in which small, double-stranded RNA molecules shut down genes in a targeted manner. While both academic and commercial labs have had lab successes with RNAi since it was shown to work in human cells in 2001, efforts to turn the technique into drugs have been slowed by difficulties in getting the RNAs to where they need to be to provide their therapeutic benefit. RNA molecules tend to degrade quickly in the body, are hard to get inside cells, and are difficult to target to the right tissues.

But MIT immunologist Jianzhu Chen and colleagues have taken a giant step toward overcoming the delivery problem. In research published in the June 8 issue of the *Proceedings of the National Academy of Sciences*, Chen's group successfully used a small polymer to deliver RNAs designed to block influenza infection into the lungs of mice. Chen injected a tiny amount of the RNA-polymer mixture into the animals' veins; the polymer carried the RNA through the bloodstream and into the lungs, reducing the amount of virus found in the animals' lungs as much as 1,000-fold. The RNAs protected the mice against both new and ongoing influenza infections, acting as either a short-term vaccine or a treatment. The MIT results are "very encouraging," says John Rossi, a molecular biologist investigating RNAi to treat HIV/AIDS at City of Hope hospital in Duarte, CA. "It really goes to show that effective systemic delivery is possible."

Eric Manning, a biotech analyst at Navigant Consulting, shares that optimism. The polymers Chen uses "seem to be more interesting to more people than we initially expected," he says. Manning believes such "carriers" are achieving better results than anticipated and may turn out to play a role in clinical applications of RNAi. Chen's work goes a step further than a similar study in the same journal that used a high-pressure injection technique to deliver flu-defeating RNAs to mice. Although that method has been widely used in mouse studies of RNAi, the pressure and volume of fluid involved would not be practical in humans.

In another experiment, Chen's group tried a different approach to deliver the RNAs: gene therapy. Instead of injecting the RNAs directly, the researchers used DNA molecules that coded for the anti-flu RNAs. Inside the mice, cellular machinery continually transcribes the DNA code into the active RNAs. To deliver the DNAs to the lungs, the researchers tested both the polymers used in the previous experiment as well as surfactant, a chemical used to prevent respiratory distress syndrome in premature babies. Both materials worked, though the polymers were more effective, yielding about

a 100-fold reduction in the amount of virus present in the lungs.

The polymers Chen used are limited: they tend to deliver their loads preferentially to the lungs. But different methods of delivering RNAi-based treatments to other parts of the body have shown promise recently as well. In two additional studies, researchers have investigated different means of using gene therapy to deliver RNAi to treat brain cancer and a neurological disorder related to Huntington's disease.

In work reported June 1 in the journal *Clinical Cancer Research*, William Pardridge of the University of California, Los Angeles, modified liposomes—essentially tiny spheres of the molecules that make up cell membranes—to target them specifically to human cancer cells implanted into the brains of mice. Two molecular homing signals called antibodies, normally produced by the immune system to fight infection, directed the liposomes first through the blood-brain barrier and then to the cancer cells. The spheres fused with the cancer cells and delivered their DNA load. The DNA encoded an RNA molecule designed to block a gene called EGFR, which runs amok in many kinds of cancer. Weekly injections more than doubled the survival time of the mice, from about 14 days to 31 days.

Pardridge's results "look pretty encouraging," says Rossi, but "there are a lot of 'ifs.'" One problem is that liposomes are mildly toxic, which could hold back their use in humans; another is the design of the study itself, which leaves open the possibility that the survival benefit resulted from a general immune reaction to the liposomes or the RNA molecules—not from a specific RNAi mechanism. While Rossi believes the technology has a "chance" of working in humans, Pardridge is convinced; he plans to develop the liposomes for use in humans through ArmaGen Technologies, a company he founded in Santa Monica, CA, to commercialize gene delivery technologies. By varying the antibodies on the surface, Pardridge says, liposomes could be targeted to any tissue in the body.

In the second study, Beverly Davidson, associate director of the Iowa Center for Gene Therapy, has used a combination of gene therapy and RNAi to treat a mouse model of an inherited nerve-destroying disease related to Huntington's. In research presented June 4 at the 2004 meeting of the American Society for Gene Therapy, Davidson employed a disabled virus to deliver RNAi-based gene therapy that blocked production of a mutant protein in the brains of mice affected by the disease, known as spinocerebellar ataxia type 1 (or SCA1). Unlike many genetic diseases in which gene therapy can "add back" a normal version of a mutated protein, so-called dominant genetic illnesses, such as SCA1 and Huntington's, have not been able to benefit from gene therapy because the mutant protein causes symptoms even if a normal copy of the protein is present. "This is the first shot at getting at these dominant genetic diseases," says Davidson, who hopes to have the technique ready to test in humans within five years. Huntington's will be the likely first target, she says.

Despite the encouraging results from these three studies, drug companies would ideally like to be able to use RNAi as a drug without any "extras" that would complicate manufacturing. Following stunning early successes, several startups were launched to develop RNAi into drugs. Several of the companies are working on a direct approach to the delivery problem: chemically modifying the RNA molecules to stabilize them in the blood and also to get them taken up into cells and tissue. "A lot of it hasn't been

published yet, but it certainly will be coming out soon,” says Rossi, who cites therapeutic companies Sequitur (now part of Invitrogen), Atugen, Sirna, and Alynlyam Pharmaceuticals as leaders in this area. “Drug companies would like to have the simplest formulation possible,” he adds. Using RNA molecules directly, he says, “would be the ultimate goal.”

Success is far from assured. Gene therapists have been trying to deliver naked DNA into cells for well over 25 years, with very limited success, says Mark Kay, director of the Program in Human Gene Therapy at Stanford University School of Medicine, who is investigating RNAi for the treatment of hepatitis. And DNA is a more stable molecule than RNA. “It’s hard to know” which delivery methods will win out, Kay says. But, he adds, “If I had to bet right now, I think I would bet on gene therapy” techniques such as Davidson’s, using viruses to deliver the therapeutic molecules.

Chances are, different methods will end up being used to treat different diseases. And regardless of the final winners, the new results offer concrete hope that biologists may finally be inching closer to delivering on the promise of RNAi.

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