Molecular Scissors: RNA Enzymes Go Commercial

A Nobel Prize–winning discovery that could revolutionize genetic engineering gets patented—but not everybody's happy

WHEN THOMAS CECH OF THE UNIVERSITY of Colorado discovered in 1982 that RNA can act as an enzyme, catalyzing specific biological reactions, the result surprised molecular biologists. Only proteins, they thought, could act as enzymes. The work not only led to a Nobel Prize for Cech, it prompted prophecies of a new kind of genetic engineering—one based on RNA instead of the conventional DNA. Foreign governments launched research efforts, and researchers scrambled to file patents. The stakes were so high that American and Australian researchers became embroiled in a dispute over patent rights for catalytic RNA.

Now some of the dust has settled and the winner is: Tom Cech. Last week the U.S. Patent Office awarded Cech and the University of Colorado an unusually broad patent for the use and synthesis of enzymatic RNA—also known as ribozymes. Indeed, the patent is so broad that it reminds some insiders of the pioneering patent awarded to Stanford's Stanley Cohen and the University of California's Herbert Boyer in 1980 for a recombinant DNA technique that became the backbone of genetic engineering. "The analogy most people are making is this is as important to RNA as the Cohen-Boyer patent was to DNA," says Steven Burrill, a biotech industry analyst for Ernst & Young. "If that's true, this patent is a very, very significant event."

Thomas A. Mann of United States Biochemical Corp. (USB), the company to which Cech sold his licensing rights, exults: "This potentially represents a class of compounds that are at least as broad in their utility as antibiotics." The applications include potential therapies for almost all the viral diseases, including possibly AIDS, hepatitis, and herpes. But in spite of the current euphoria, concern lingers—on the part of those who worry that Cech's patent is so broad that it could inhibit the field.

The significance of the patent stems from Cech's unexpected observation that preribosomal RNA can cut and splice itself, removing sequences not needed for biological function. Says Cech: "Ribozymes have the ability to act as a sort of molecular scissors." Those findings were complemented by work from Sidney Altman at Yale, who showed that transfer RNA could be cut by another, separate piece of RNA in conjunction with a protein, and that the job could be done over and over—as enzymes work. For that work, Cech and Altman shared the 1989 Nobel Prize in chemistry.

The practical ramifications were startling. Researchers wielding those scissors could now manipulate RNA as easily as they had learned to manipulate DNA. They could synthesize or purify bits of catalytic RNA and use them to snip the RNA of threatening viruses, bacteria, and fungi that cause disease in humans and plants—or to destroy viruses that prey on crops. "RNA is at the heart of all viral and many other diseases in man," says Cech. "Even DNA viruses must make their own particular messenger RNA to be infectious."

The RNA scissors are remarkably precise, honing in on and snipping out specific sequences of foreign RNA, which can then be disposed of by other enzymes in the cell. Early research by John Rossi at the Beckman Research Institute of the City of Hope has shown that so-called hammerhead ribozymes can disarm the AIDS virus—at least in culture—by cleaving its genetic material, which is RNA. Ribozymes also are effective against the tobacco mosaic virus in plants.

The anticipation of winning the patent prompted USB to start work on several ribozyme products, and the company hopes to go into clinical trials next year with a ribozyme for treating herpes skin lesions in humans. USB also is discussing joint ventures with major pharmaceutical firms and biotechnology companies, which hope to use ribozymes to develop drugs to treat and diagnose AIDS, hepatitis, and other diseases in humans, and to develop products that would protect plants from disease and predators.

Despite their promise, there are technological challenges to overcome before ribozymes make it out of the lab. Researchers need to learn how to get RNA scissors into cells and also how to make sure the synthesized bits of RNA remain chemically stable long enough to do their job. And before they are used in human beings, some remaining questions about the precision of these RNA scissors will have to be settled, such as whether they snip the wrong place. "RNA scissors work in the lab real well," says Cech. "We now have the challenge to see if they can work in a real-life situation."

And beyond the scientific applications, there are questions about whether the patent granted to Cech will be good for the field—or whether it is so all-encompassing that further proposals for commercial application of ribozymes will be subsumed under it.

That question could be given a test soon—a test growing out of a three-year-old dispute between Cech's group and scientists at the Commonwealth Scientific and Industrial and Research Organisation (CSIRO), an Australian government lab. Scientists there have filed their own patent in Australia for the use and synthesis of a ribozyme they claim is different from—and more specific than—Cech's. But USB's officials and Cech believe that the Australian group's ribozymes are covered under their patent. CSIRO's official response: "We were confident of the strength of our position [when they filed their patent] and remain so now."

Not everyone is so confident. Even Altman, co-winner of the Nobel Prize, could be left out. "When one hears of people writing patents so broad that they seem to exclude the entry of anyone else into a particular field, it's not healthy for the research enterprise," says Altman, who has sold his potential licensing rights to a company called Innovir, which has a patent pending.

Other researchers say, however, that there are so many opportunities for using ribozymes that there are sure to be new patents. "Cech's work obviously was a fabulous piece of science," says biotechnology patent attorney Tom Ciotti. "The question is, will the patent really cover everything that flows out it? The answer is no—there will always be room for other people."

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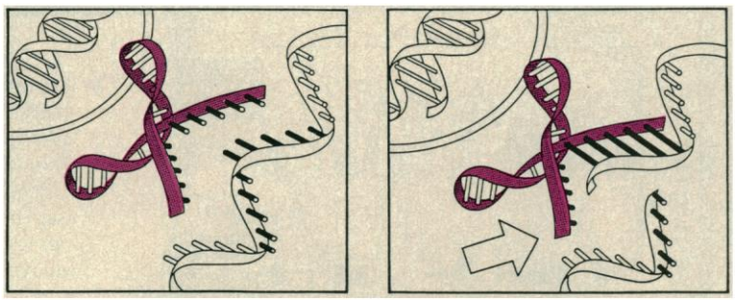

Cut-and-paste. *A small RNA segment* (color) *can act as an enzyme—clipping another piece of RNA.*