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CHEMICAL MANIPULATION SPEEDS UP IDENTIFICATION OF GENES

DALLAS – Nov. 25, 1996 – Scientists at UT Southwestern Medical Center at Dallas have shown that genetic probes can be modified to accelerate recognition of DNA sequences and increase the strength of their binding.

The probes, known as oligonucleotides, are short manmade pieces of DNA-like molecules, and engineering improvements in their properties eventually could make clinical testing for inherited diseases faster, said Dr. David Corey, UT Southwestern pharmacology assistant professor and Howard Hughes Medical Institute assistant investigator. The research is reported in *Nature Biotechnology's* December issue.

DNA is negatively charged and will repel unmodified DNA-based gene probes because these are also negatively charged. This limits the ability of probes to recognize DNA sequences within genes rapidly.

To avoid this problem, the UT Southwestern scientists used oligonucleotides stripped of their negative charge or which had a positive charge attached. These neutral molecules were not repelled by DNA while searching for a matching sequence, allowing them to bind faster and more tightly, Corey said.

Such altered oligonucleotides should facilitate identification of genetic changes that determine an individual's inherited traits and diseases.

"DNA recognition is important for diagnosing genetic diseases because those are caused by a change in the DNA," Corey said. "You bring in a small piece of DNA to find out if a change is actually there or not. In the next 10 years, in the average doctor's office, physicians will be able to test people for a whole range of genetic diseases. That will be done by oligonucleotides recognizing complementary sequences."

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He said these methods of altering oligonucleotides will make gene identification easier and more efficient.

"What we've shown is that you can manipulate the charge on the probe to increase the speed at which you can identify genes," he said.

This means current methods of gene identification would take an hour to accomplish what modified oligonucleotides would do in 30 seconds. In addition, it takes less DNA for the test, and the sample will last longer because it can't be changed by enzymes.

"On the diagnostic side of genetic testing, this is a very important tool," Corey said. "On the therapeutic side, it's been a great dream of a lot of scientists to develop a magic bullet that can target any gene. That would be wonderful. Oligonucleotides offer that possibility because they can, in theory, recognize any sequence.

"But that has been impossible because the chemical makeup hasn't been favorable. Everything I've seen says that the neutral oligonucleotides can target specific genes. Once scientists know how to get them into cells, we'll be able to ask the important question: 'How well do they turn genes on or off?'"

Although other methods now are used to locate genes using oligonucleotides, they are much slower and less efficient than the chemically altered molecules, he said. It's important for scientists to realize that these gene-searching molecules – neutral oligonucleotides – are easy to make, easy to use, and are a practical, realistic way of making genetic research more efficient and faster.

Other researchers involved in this study are Howard Hughes Medical Institute (HHMI) associate Dr. Sergey Smulevitch, HHMI research technician Carla Simmons, and UT Southwestern graduate students James Norton and Teresa Wise.

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