SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS MAY HAVE NEW TARGET FOR CANCER DRUGS

DALLAS — May 1, 1996 — The tip that keeps chromosomes from unraveling may also be the bull's eye for cancer drug therapy.

In the May issue of *Nature Biotechnology*, researchers from UT Southwestern Medical Center at Dallas report on experiments in which a specific type of molecule was used to stop the enzyme telomerase from functioning.

Telomeres are at the tips of the chromosome, and telomerase is the enzyme required to maintain their length. In normal cells, telomeres become shorter each time the cell divides. Eventually, they become so short that a cell can no longer divide and the cell line dies out. Telomerase activity appears to be an early and important indicator of cancer cell development.

Dr. David Corey, an assistant professor of pharmacology and assistant investigator in the Howard Hughes Medical Institute at UT Southwestern, and his colleagues used a peptide nucleic acid (PNA) to bind to a portion of the telomerase and inhibit its function in human breast cancer cells.

"Our conclusion suggests that the inhibition of telomerase may be a viable strategy for limiting tumor growth in humans," Corey said.

Corey's collaborators included Drs. Jerry Shay and Woodring Wright, both professors of cell biology and neuroscience at UT Southwestern.

Previous work by Shay and Wright has demonstrated that telomeres shorten in normal cells but maintain their length in almost all human cancer cell lines. This correlates with inappropriate expression of telomerase and, as a consequence, allows the cell to become "immortal." Cell immortality is a critical step for almost all cancers to progress.

Many investigators believe the ability to measure and perhaps alter telomere length

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and/or telomerase activity may in the future give physicians new diagnostic and treatment tools for managing the care of patients with cancer. Attacking cancer cells with a PNA-based drug is an example of how that theory could be applied.

But Corey said PNAs also have problems as potential drug couriers. Primarily, the PNAs are not built to cross cell membranes, where drugs need to go to do their job. Finding out how to get PNAs into a cell is one of the next steps of Corey's research.

Corey was able to overcome that problem in the current study by using an assay that Shay and Wright developed to open up the cell. This allowed Corey to deliver the PNA directly to the telomerase residing in the cell and block its activity.

PNAs have characteristics that make them ideal for binding to telomerase. "PNAs are very attractive as a drug-delivery system," Corey explained, "because they are highly selective in where they bind and because they bind tightly to the targeted molecule. This gives us the potential to target an enzyme that is potentially very important in cancer cell growth and to cause the cell to stop working."

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