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UTSW researchers identify new potential target for cancer therapy

DALLAS – April 22, 2013 – UT Southwestern Medical Center researchers have found that alternative splicing – a process that allows a single gene to code for multiple proteins – appears to be a new potential target for anti-telomerase cancer therapy.

The enzyme telomerase is overexpressed in almost all cancer cells, and previous research efforts have failed to identify good telomerase inhibitors. The study by Dr. Woodring Wright and UT Southwestern colleagues in the April 4 issue of *Cell Reports* identifies a new approach for inhibiting telomerase, which is an enzyme that drives uncontrolled division and replication of cancer cells.

Alternative splicing allows genetic information to be assembled in different ways and is almost always controlled by DNA sequences that are immediately adjacent to the parts of a gene that code for protein. “In the case of the telomerase gene, we found that these controlling regions are located very far from the protein coding regions and that they contain unusual DNA sequences,” said Dr. Wright, professor of cell biology and internal medicine. “Their unusual DNA structure suggests that humans regulate telomerase in a very different fashion that we may be able to exploit to develop inhibitors of the enzyme.”

Most of the splice variants that telomerase makes are inactive, but Dr. Wright’s team demonstrated that it was possible to shift the splicing to make even less active telomerase, potentially providing a new approach for cancer therapy.

Telomeres are specialized structures at the ends of each chromosome. As DNA replicates, telomeres shorten each time a cell divides. Telomerase in human cancer cells is 10 to 20 times more active than in normal body cells. The increase provides a selective growth advantage to many types of tumors. If telomerase activity was to be turned off, then telomeres in cancer cells would shorten like they do in normal body cells.

“The oft-used analogy is that telomeres are like the plastic ends of shoelaces that protect them from fraying,” Dr. Wright said. “Once the plastic becomes damaged and falls off, the shoelace can no longer be threaded effectively. The only solution at that point is to throw the shoelace away.”

In most tissues, telomerase turns off during development, after which telomeres shorten and limit the number of times a cell can divide, eventually losing their capping function similar to the

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shoelace tip falling off. This timing also functions as a tumor-protection mechanism, since the limited cellular lifespan prevents pre-malignant cells from accumulating the mutations they need to become cancerous.

Preclinical studies have shown that inhibiting telomerase causes tumor cells to lose immortality, re-initiate telomere shortening, and eventually die. In the event that a tumor has already thoroughly developed, it may be surgically removed, and following conventional chemotherapy, telomerase inhibition could prevent rare surviving cells from having enough divisions to cause a relapse.

Dr. Wright said the alternative splicing method also could be useful for regenerative medicine, because telomeres in our stem cells shorten with age and that eventually compromises their function. “Under the right circumstances, increasing or decreasing telomerase activity could profoundly affect our treatments for both cancer and aging,” he said.

The investigation was supported by the National Cancer Institute.

Other UT Southwestern researchers participating in the study are graduate student Sze “Mandy” Wong, who served as first author; research associate Ling Chen; medical student Radhika Kainthla; and Dr. Jerry Shay, professor of cell biology and a senior member of the Harold C. Simmons Cancer Center.

Please visit the [Harold C. Simmons Cancer Center](#) to learn more about oncology at UT Southwestern, including highly individualized treatments for cancer at the region’s only National Cancer Institute-designated center.

About UT Southwestern Medical Center

UT Southwestern, one of the premier academic medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. The institution’s faculty has many distinguished members, including five who have been awarded Nobel Prizes since 1985. Numbering more than 2,700, the faculty is responsible for groundbreaking medical advances and is committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 100,000 hospitalized patients and oversee more than 2.1 million outpatient visits a year.

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