SOUTHWESTERN NEWS

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SCIENTISTS CAUSE HUMAN CANCER CELL DEATH BY INHIBITING TELOMERASE

DALLAS –December 7, 1999 – Scientists at UT Southwestern Medical Center at Dallas caused the death of human cancer cells by inhibiting telomerase – the enzyme capable of immortalizing human cells. They developed small synthetic inhibitors against telomerase that when introduced into human cancer cells caused progressive telomere shortening and eventually cell death.

The study, published in today's issue of the *Proceedings of the National Academy of Sciences*, validates telomerase as a target for anti-cancer drug therapy.

Dr. David Corey, Dr. Jerry Shay and collaborators designed nucleotide sequence inhibitors to interact with complementary sequences in the telomerase gene, thereby preventing its activity. These inhibitors led to the progressive shortening of telomeres in human breast and prostate cancer-cell lines grown in the laboratory. The researchers also showed that if the inhibitor was withdrawn, the telomeres regained their initial lengths.

"The use of anti-telomerase synthetic inhibitors should open up a new class of therapeutic cancer drugs that will have a powerful role in cancer therapy," said Shay, professor of cell biology. "They should prevent the recovery of residual cancer cells following conventional therapy and thus make them more susceptible to attack by the immune system or killing by existing therapeutic agents."

Telomerase activity is widely recognized as a marker of cancer cells, and its activity has been correlated with tumor aggressiveness in a number of studies. While most normal cells have finite life spans and do not contain telomerase, more than 90 percent of cancer cells, which divide indefinitely, contain telomerase.

Previous work (*Science* 279:349-52, 1998) by Shay; Dr. Woodring Wright, professor of cell biology; other UT Southwestern co-workers; and Geron Corp. colleagues proved that telomerase was sufficient to immortalize normal human cells grown in the laboratory and that progressive shortening of telomeres – specific short pieces of deoxyribonucleic acid (DNA) that telomerase adds back to the ends of chromosomes – is the biological clock that governs how

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many times a cell divides.

Because telomerase has an essential ribonucleic acid (RNA) component that acts as a template for adding back telomeres to the ends of chromosomes, Corey and colleagues designed short pieces of RNA and DNA to bind to the telomerase RNA template and block the enzyme's activity. These synthetic inhibitors belong to a family of molecules already being tested in clinical trials for other diseases.

"Using the synthetic inhibitors we designed, we are confident that the effects we observed are due to the inhibition of telomerase," said Corey, associate professor of pharmacology and biochemistry. "This opens the door to the next step – rational and well-controlled animal studies."

In theory telomerase inhibition should prevent the addition of new telomeres but not cause immediate cell death. With each successive cell division, the telomere length should decrease – as seen in normal human cells that have no telomerase – until due to shortened telomere length, the cells die. The time between addition of the inhibitor and cell death should depend on the initial telomere length– the shorter the telomere length, the sooner cell-growth inhibition is achieved.

"In the experiment, which was carried out for over 100 days, no cells survived the anti-telomerase treatment. In most current cancer therapies, there are often some tumor cells that survive the initial treatment, and this can often lead to cancer relapses," Shay said. "Since no cells survived in the study, this indicates that alternative mechanisms to maintain telomere length were not easily activated."

Other UT Southwestern investigators participating in the study were lead co- authors cell biology postdoctoral fellow Dr. Brittney-Shea Herbert and molecular biophysics graduate student Anne Pitts; research technician Scott Baker and research associate Susan Hamilton, both of the Howard Hughes Medical Institute; and Wright.

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