SOUTHWESTERN NEWS

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SCIENTISTS EXTEND THE LIFE SPAN OF HUMAN CELLS

DALLAS – Jan. 16, 1998 – Researchers at UT Southwestern Medical Center at Dallas and their colleagues at Geron Corp., Menlo Park, Calif., say they have figured out how to overcome the mechanisms that control cellular aging and extend the life span of human cells.

In the Jan. 16 issue of *Science*, Drs. Woodring Wright and Jerry Shay, UT Southwestern professors of cell biology and neuroscience, and their collaborators report finding that the enzyme telomerase — which UT Southwestern scientists call a "cellular fountain of youth" — causes human cells grown in the laboratory to retain their "youth" and continue to divide long past the time when they normally stop dividing.

Normal human cells have a limited capacity to proliferate. After a certain finite number of cell divisions, time on the biological clock runs out; the cells "age" and stop dividing. Time remaining in a cell's life correlates with the length of the telomeres — repeated sequences of DNA on the ends of chromosomes that protect the tips from degradation. In normal cells, telomeres shorten with each cell division. Although some have thought that this telomere shortening might be the biological clock's control mechanism, the hypothesis was controversial. The research now proves that human cells grow older each time they divide because their telomeres shorten.

Specialized reproductive cells and most cancer cells appear to divide indefinitely. They contain the enzyme telomerase, which adds back telomeric DNA to the ends of chromosomes. Most normal cells do not have this enzyme.

"We have found that cellular aging can be bypassed by the introduction of the catalytic component of the immortalizing enzyme telomerase," Shay said. "The expression of telomerase

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in normal human cells should extend their lifespan indefinitely. From a basic research point of view, we could begin to replace the abnormal tumor-cell lines now being used to study biochemical and physiological aspects of growth and differentiation with normal, yet immortal cell lines."

The scientists introduced telomerase into normal human cells to see if the cells' life spans could be prolonged. The cells with telomerase extended the length of their telomeres, divided for 20 additional generations past the time they normally would stop dividing and are continuing to divide. The cells also grew and divided in a normal manner, giving rise to normal cells with the normal number of chromosomes. By all accounts these cells had found their fountain of youth.

"The extension of normal cell lifespan in a youthful state by telomerase is a dramatic confirmation of the telomere hypothesis and one that presents numerous opportunities for biotechnology and medicine," said Dr. Calvin Harley, Geron vice president and chief scientific officer.

One immediate use of finding that telomere shortening controls cellular aging may be in the area of producing engineered products in human cells. Instead of using uncharacterized primary human-cell cultures to produce vaccines or other biological products, one should now be able to produce products in a re-engineered normal human cell-type that does not change, Wright said.

"This research raises the possibility that we could take a patient's own cells, rejuvenate them, then modify the cells as needed and give them back to the patient to treat a variety of genetic and other diseases," Wright said. "The potential long-term applications are simply staggering."

Other investigators on the project included Drs. Andrea Bodnar, Maria Frolkis, Choy-Pik Chiu, Gregg B. Morin, Calvin Harley and Serge Lichtsteiner of Geron Corp.; and Drs. Michel Ouellette and Shawn Holt, research fellows in UT Southwestern's Department of Cell Biology and Neuroscience. The research was funded in part by the National Institutes of Health.

The investigators' website can be found at: www.swmed.edu/home_pages/cellbio/shay/

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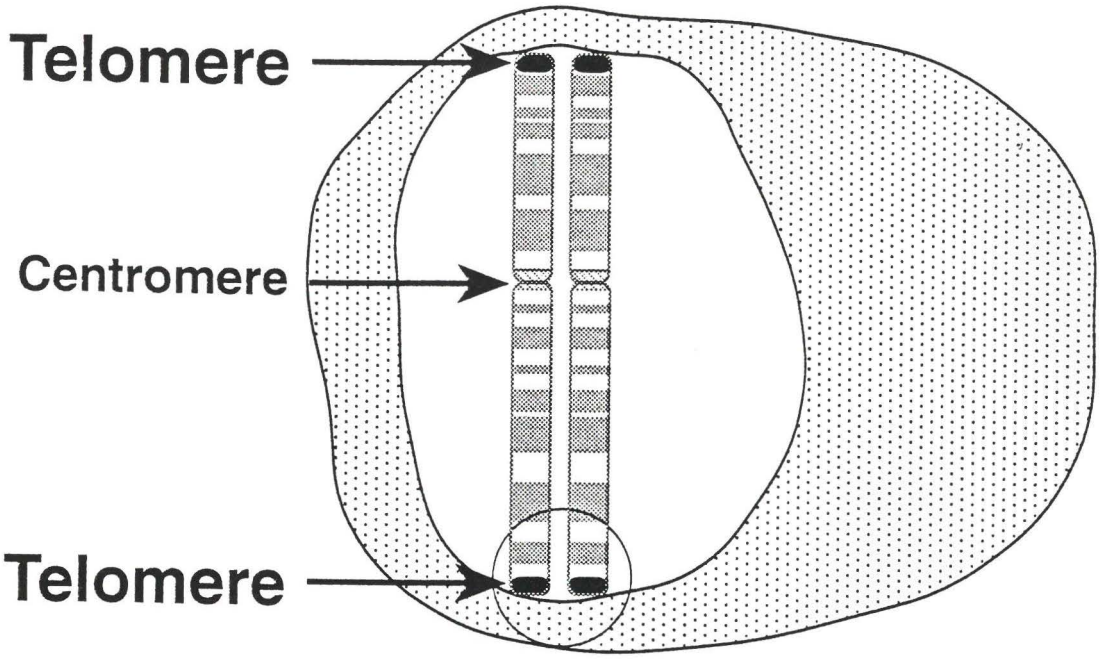
CHROMOSOMES IN THE NUCLEUS OF A HUMAN CELL



Telomeres, repeated sequences of DNA on the ends of chromosomes, are special structures that protect the chromosome tips from degrading. Some telomeric DNA is lost with each cell division, which eventually causes the cell to age. Researchers at UT Southwestern Medical Center at Dallas and Geron Corp. have shown that extending the length of telomeres of human cells grown in a lab avoids aging and enables cell to retain their "youth."