SOUTHWESTERN NEWS

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RESEARCHERS DISCOVER TUMOR-SUPRESSOR GENE THAT MAY INDICATE SUSCEPTIBILITY TO LUNG AND COLON CANCER

DALLAS — Oct. 9, 1998 – Discovery of a new human tumor-suppressor gene by UT Southwestern Medical Center at Dallas researchers could dramatically reduce the number of Americans who die annually from the two most lethal cancers, lung and colon malignancies.

Defining the *PPP2R1B* gene in human lung and colon cancer could make it possible for doctors to accurately predict who has a high risk of developing the two illnesses and find effective therapies for those already afflicted. The study is reported in today's journal *Science* by a team of investigators led by Dr. Glen Evans, director of the Eugene McDermott Center for Human Growth and Development at UT Southwestern, and Dr. Steven Wang, a postdoctoral fellow in the center.

"This finding is exciting because we have been able to locate, identify and determine the functions of this gene that is involved in lung and colon cancer and probably many others," said Evans, who also directs the Genome Science and Technology Center. "The mutations we found are both somatic and germline, in other words, found in both normal and tumor tissue. The significance of this evidence means the defect may be inherited, making some people more susceptible to cigarette smoke and similar tumor-promoting chemicals."

The American Cancer Society estimates that in 1998 nearly 48,000 people will die of colon cancer and 160,000 of lung cancer. Scientists already know that tumor promoters effect a biochemical process that is involved with phosphate metabolism.

PPP2R1B makes one of three proteins that removes phosphates from protein molecules that regulate cell growth. If the gene is not working correctly, too much phosphate builds up on the

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regulatory proteins, and the growth becomes uncontrolled. This unchecked cell division is the beginning of a tumor.

The researchers found *PPP2R1B* on chromosome 11 in an area they call a "hot spot" for cancer genes. They knew where to find the area because in many tumors a small section of chromosome or a gene is missing. This is called loss of heterozygosity (LOH).

Using a computer and gene sequences found through the international Human Genome Project, Wang checked about 100 genes in the LOH region until he found *PPP2R1B,* which appeared to be a cancer-suppressing gene, one that removes phosphates to control cell growth.

Next investigators used cells from people never diagnosed with cancer and from the normal tissue and the tumor tissue of cancer patients to test for mutations in *PPP2R1B*. They found that in the tumor tissue something had gone wrong with *PPP2R1B* so that additional phosphates were being added to the proteins allowing the cells to grow.

"If we can affect the amount of phosphates on these proteins through gene therapy or with a new drug, then we could arrest cell growth," said Evans, who holds the Eugene McDermott Distinguished Chair for the Study of Human Growth and Development. "We also now have the potential to predict who will get cancer from smoking and who won't."

The other researchers involved in this study included: Edward Esplin, UT Southwestern medical student and McDermott Center pre-doctoral student; Jia Ling Li, McDermott Center research scientist; Liying Huang, McDermott Center research assistant; Dr. Adi Gazdar, professor of pathology; and Dr. John Minna, director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics.

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