SOUTHWESTERN NEWS

SCIENTISTS DEVELOP NEW TOOL FOR FUNDAMENTAL STUDY OF CANCER

DALLAS—June 25, 1993—Researchers at The University of Texas Southwestern Medical Center at Dallas and at Genentech Inc. have designed a molecule that may stop uncontrolled cell division in certain kinds of tumor cells. Genentech is a California biotechnology firm.

Nobel laureates Drs. Michael S. Brown and Joseph L. Goldstein and colleagues at UT Southwestern and Dr. James C. Marsters Jr. and colleagues at Genentech report in the June 25 issue of Science on research that has resulted in development of a family of benzodiazepine-based "peptidomimetics" that inhibit an enzyme vital to the function of oncogenic *Ras* proteins.

"These compounds will allow us to test the theory that inhibition of the enzyme that turns *Ras* on could be effective in stopping the growth of certain tumors," Brown said.

Normal *Ras* is found in all normal tissues, but oncogenic *Ras* has been implicated as a contributing factor in some colon cancers and in almost all cancers of the pancreas.

Goldstein and Brown emphasized that this is neither a new treatment nor a cure for cancer. "This is one step in what may be a very long process that may eventually lead to the design of new treatments for certain types of cancer," Goldstein said.

Ras is a protein inside cells that helps control cell division. When one cell signals another to divide, the cell receiving the signal activates *Ras*. But before *Ras* can pass along the signal to divide, a fatty substance in the cell called farnesyl—a building block of cholesterol—must attach to the protein. Once farnesyl has attached to *Ras* in a process called farnesylation, *Ras* can attach to the inner

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surface of the cell's plasma membrane, where it can perform its normal function of transmitting the signal to a cell to divide.

Normally *Ras* switches back and forth between an active and inactive state. But if there has been a mutation in the *Ras* gene, the protein may remain active. Then *Ras* keeps telling the cell to divide again and again.

Scientists have long thought that if they could find a way to prevent oncogenic *Ras* from being activated—without disturbing the normal process of cell division—they might be able to stop the growth of certain kinds of tumors.

"We knew there had to be a catalyst, an enzyme that causes farnesyl to attach to *Ras*," said Brown. "If you could find a way to block the action of that enzyme, you might be able to halt the uncontrolled cell division."

Brown and Goldstein began by looking for that enzyme.

In 1990 a postdoctoral fellow in their lab at UT Southwestern purified the enzyme, farnesyltranferase. Then Brown and Goldstein were able to isolate the gene that encodes for that enzyme.

They learned that the enzyme recognizes *Ras* proteins by a distinctive peptide sequence of four aminoacids that occurs at the extreme end of the *Ras* protein. They were able to block the action of the enzyme and prevent farnesylation in vitro, Brown said, by using a peptide with the same aminoacid sequence as the one farnesyltransferase recognizes in *Ras*.

"We used a peptide as a Trojan horse and fooled the enzyme into attaching the farnesyl to the peptide instead of *Ras*," Brown said.

But peptides can't enter cells, so the next step was to design a peptide substitute that could enter cells but looked and worked exactly like the four-amino-acid peptide that farnesyltransferase recognizes in *Ras*.

Working with the Dallas scientists, researchers in the bioorganic chemistry department at Genentech combined efforts in peptide synthesis, molecular modeling and medicinal chemistry to develop compounds using a benzodiazepine framework that mimic the structure of *Ras*' tetrapeptide "name tag."

The benzodiazepine peptidomimetics did inhibit the action of farnesyltransferase, effectively blocking up to 90 percent of cell growth in

cells from rats transfected with a mutated *Ras* gene. They blocked uncontrolled proliferation without preventing normal cell division.

"We now have something that moves from the test tube to tissue culture," Goldstein said. "The next step is to test it in mice with tumors."

Goldstein, chairman of molecular genetics at UT Southwestern, is holder of the Distinguished Chair in Biomedical Science and the Paul J. Thomas Chair in Medicine.

He and Brown won the 1985 Nobel Prize in physiology or medicine for their work on the molecular mechanism of cholesterol metabolism.

Director of UT Southwestern's Erik Jonsson Center for Research in Molecular Genetics and Human Disease, Brown is holder of the W.A. (Monty) Moncrief Distinguished Chair in Cholesterol and Arteriosclerosis Research and the Paul J. Thomas Chair in Medicine.

First author on the Science paper is Dr. Guy L. James, postdoctoral fellow in molecular genetics at UT Southwestern and recipient of a fellowship from the Helen Hay Whitney Foundation.

Authors from Genentech, in addition to Marsters, include Drs. Thomas E. Rawson, Todd C. Somers and Robert S. McDowell from the bioorganic chemistry department: and Drs. Craig W. Crowley, Brian K. Lucas and Arthur D. Levinson from the cell genetics department.

Scientists at Merck Research Laboratories of West Point, Pa., report in the same issue of Science on the development of a different type of peptide analog that also inhibits farnesyltransferase and slows the growth of tumor cells in tissue culture.

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NOTE: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences, Southwestern Allied Health Sciences School, affiliated teaching hospitals and outpatient clinics.