UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

**EMBARGOED UNTIL 4 P.M. CDT MONDAY OCT. 9, 2006**

## Study reveals mechanism for cancer-drug resistance

DALLAS – Oct. 9, 2006 – Using the worm *Caenorhabditis elegans*, researchers at UT Southwestern Medical Center have discovered a mechanism by which cancer cells become resistant to a specific class of drugs.

They found that a mutation in a single protein in the worm renders a potential new cancer drug ineffective. The drug is a derivative of a compound called hemiasterlin. Because hemiasterlin compounds are being tested as a way to fight multi-drug resistance, this newly discovered resistance effect is problematic, the researchers said.

"A major problem for cancer therapy is that if cancer cells can survive long enough, they have a chance to undergo mutations that make them resistant to anticancer drugs," said Dr. Michael Roth, professor of biochemistry and senior author of a paper published this week in the online edition of the *Proceedings of the National Academy of Sciences.*

One way that cancer cells resist multiple drugs is through the action of the multi-drug resistance protein, which pumps most drugs out of the cell before they can have any effect.

However, hemiasterlin bypasses this pump altogether and kills cancer cells by preventing them from dividing.

Derivatives of hemiasterlin are being tested as anti-cancer therapies, with one already in clinical study. The drug works by interfering with tubulin, which forms the structure that separates chromosomes as cells divide.

"One of the properties of hemiasterlin that makes it attractive as a potential therapeutic is that it remains very toxic for cancer cells that express the multi-drug resistance protein, which is a major mechanism of drug resistance in cancer," said Dr. Roth.

The UT Southwestern researchers sought to pin down the action of hemiasterlin, so they worked with the tiny research worm *C. elegans*, which is often used for genetic studies but not often used to test drugs.

The researchers created a large population of mutant worms and isolated eight that were

(MORE)

resistant to derivatives of hemiasterlin. They then focused on a single mutant worm in order to investigate why it was resistant to the anti-cancer drug.

Genetic analysis showed that this resistant worm had a single mutation in the gene for a protein called prohibitin 2. Prohibitin proteins are thought to be involved in several functions in normal cells, including proliferation, aging, tumor suppression and protein folding.

The mutation also made these worms resistant not only to hemiasterlin but also to several other anti-cancer drugs that interfere with tubulin.

Further studies will focus on the other strains of mutant worms to determine whether the anti-cancer drugs that attack tubulin use mechanisms similar to hemiasterlin.

These types of studies can reveal how a drug works, perhaps picking up side effects before it becomes used widely, Dr. Roth said.

Other UT Southwestern researchers involved in the study were Iryna Zubovych, research assistant in biochemistry; Thomas Doundoulakis, a former graduate student now at UT Arlington; and Dr. Patrick Harran, professor of biochemistry.

The work was supported by the National Cancer Institute.

###

**About UT Southwestern Medical Center**

UT Southwestern Medical Center, one of the premier medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. Its more than 1,400 full-time faculty members – including four active Nobel prize winners, more than any other medical school in the world – are responsible for groundbreaking medical advances and are committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 89,000 hospitalized patients and oversee 2.1 million outpatient visits a year.

###