UT SOUTHWESTERN MEDICAL CENTER NEWS

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

EMBARGOED UNTIL NOON CDT, WEDNESDAY, APRIL 11, 2007

Massive gene screening points way to more effective chemotherapy

DALLAS – April 11, 2007 – Using a technology that can quickly screen all 20,000-plus human genes for biological activity, scientists have isolated 87 genes that seem to affect how sensitive human cancer cells are to certain chemotherapy drugs.

In a study available online and appearing in the April 12 edition of the journal *Nature*, researchers at UT Southwestern Medical Center describe how they used a library of small RNA molecules – the first used by a university research center – to identify the genes.

When the researchers blocked the action of some of the 87 genes inside isolated lung-cancer cells, they found that those cells were up to 10,000 times more sensitive to the chemotherapy drug paclitaxel (Taxol).

The results are important because the ability to lower the dose of chemotherapy drugs without compromising effectiveness reduces debilitating side effects, said Dr. Michael White, professor of cell biology at UT Southwestern, associate director for basic science at the Simmons Comprehensive Cancer Center, and senior author of the study.

"Chemotherapy is a very blunt instrument," he said. "It makes people sick, and its effects are very inconsistent. Identifying genes that make chemotherapy drugs more potent at lower doses is a first step toward alleviating these effects in patients."

The current study tested only isolated cancer cells, so further studies will be needed to determine whether blocking the genes in living animals has the same effect.

The findings were made possible because of a technology that allows scientists to rapidly test how cells react when a given gene is turned off, or "silenced." The so-called high-throughput employs a series of small plastic dishes, each with 96 wells. Using a robot, researchers place small bits of RNA that can block the function of one gene into each well on the plate. Next, non-small-cell lung cancer cells are placed in each well with the RNA.

The tiny bits of RNA used are called small interfering RNA, or siRNA. In this experiment, four siRNAs targeting a single gene were placed in each well. Overall, the researchers used 84,508

(MORE)

different siRNAs.

Next, the drug paclitaxel was added to each well for two days. By examining the survival of the cells in each well, the researchers determined which genes were involved in affecting the cells' sensitivity to the drug.

All told, the experiment took more than 150,000 individual pipetting steps over seven weeks to test the drug.

The researchers then re-tested the six genes that showed the most dramatic effect with paclitaxel and tried the same test using the chemotherapy drugs vinorelbine (Navelbine) and gemcitabine (Gemzar), but the results were not as dramatic as those seen for paclitaxel. "Our studies using additional drugs indicate that the genes we uncovered are highly specific for paxlitaxel," said Dr. Angelique Whitehurst, postdoctoral researcher in cell biology and lead author of the study.

"Being able to do this in human cells, and being able to do it fast – this is very powerful," Dr. White said. "The idea of the screen was to be able to take advantage of the new generation of technology to silence any gene we want. That's the power of a genome-wide screen – you go in without any expectations and let the data tell you what's important."

The siRNA library was developed by Dharmacon Pharmaceuticals and is commercially available. UT Southwestern is the first academic research institution to publish a study using the library, Dr. White said.

Other UT Southwestern researchers involved in the study were Brian Bodemann, medical and graduate student; Jessica Cardenas, student research assistant; Dr. Luc Girard, assistant professor of pharmacology in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research; Dr. Michael Peyton, research scientist in the Hamon Center; Dr. John Minna, professor of internal medicine and director of the Hamon Center; Dr. Carolyn Michnoff, former instructor of biochemistry; Dr. Weihua Hao, software systems specialist in biochemistry; Dr. Michael Roth, professor of biochemistry; and Dr. Xian-Jin Xie, associate professor of clinical sciences. Dr. Deborah Ferguson of Reata Pharmaceuticals also contributed to the study.

The work was supported by the National Cancer Institute, The Robert A. Welch Foundation, Susan G. Komen Foundation, and the Department of Defense.

(MORE)

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 nearly 1,500 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 about 92,000 hospitalized patients and oversee 1.7 million outpatient visits a year.

###