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STUDY IDENTIFIES WHICH PATIENTS WILL NOT RESPOND TO TREATMENT WITH TARGETED CANCER DRUG

LOS ANGELES (August 8, 2005) – By the time the human genome was mapped, cancer researchers had already begun investigating the proteins that were encoded by these newly identified genes. As the molecular engines that control all functions of the body, scientists wanted to find out how proteins work to promote health, or malfunction to cause disease. Subsequently, their discoveries have led to the development of a whole new arsenal of therapies designed to target proteins in cancer cells. But not all patients respond to treatment with these targeted drugs, prompting researchers to look for molecular clues within tumor cells that cause resistance to treatment.

Now, cancer researchers at Cedars-Sinai Medical Center have identified a protein called EMP-1 that is present in the tumors of patients who fail to respond to treatment with gefitinib, or Iressa™, a drug that has limited success in the treatment of patients with non small-cell lung cancer – the most common and deadly form of lung cancer. The study, conducted in both laboratory tests and patients with advanced non small-cell lung cancer who were treated with gefitinib, is published on-line during the week of August 8 – 12, in an “Early Edition” of the *Proceedings of the National Academy of Sciences*, and may ultimately help physicians identify patients who would benefit from treatment with gefitinib.

“Our results show that the EMP-1 protein is a biomarker for resistance to treatment with gefitinib and may enable us to identify patients who won’t respond to the drug,” said David Agus, M.D., senior author of the study and Research Director at the Louis Warschaw Prostate Cancer Center at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center. “If we know who won’t respond, we can explore other treatment options sooner and use gefitinib, when patients will benefit. This means we will be able to maximize use of this drug and treat more patients effectively.”

Gefitinib is a drug approved by the Food and Drug Administration to treat patients with NSCLC only after conventional treatment with chemotherapy has failed. It is taken in pill form and works by blocking the action of a key growth-signaling pathway in a protein called the epidermal growth factor receptor (EGFR). But gefitinib shrinks tumors in only about 11 percent of patients with non small-cell lung cancer, and most of these patients eventually develop resistance to the drug.

Given the limitations of gefitinib, scientists began looking for proteins within non small-cell lung cancer tumor cells that might indicate who would be most responsive to the drug. The first of their efforts resulted in two important studies published early last year that identified specific mutations within the EGFR pathway linked to patient response to gefitinib. However, these mutations correlated only with a partial or complete response to gefitinib in NSCLC patients, while 30 percent or more of the patients receiving the treatment reported stable disease.

“While these observations are very important, they still pose vast imprecision in predicting which patients would benefit from treatment with gefitinib, and emphasize the need for understanding the mechanisms responsible for gefitinib resistance,” said Anjali Jain, Ph.D., the first author of the study and a research scientist at Cedars-Sinai Medical Center.

To identify the proteins involved in resistance to gefitinib, the researchers first developed a resistant tumor model in the laboratory. This was done by implanting a type of prostate cancer in mice that was “androgen-independent,” or that was resistant to treatment with hormone blocking drugs and grew independently of testosterone production. The researchers chose prostate cancer tumors for this study because, similar to non small-cell lung cancer, prostate cancer tumors become resistant to treatment, have the same EGFR protein-signaling pathway and have been found to respond to treatment with gefitinib in early clinical trials and laboratory studies.

The mice were then treated with 100 mg/kg of gefitinib for five days per week. Every three weeks thereafter the tumors were removed and implanted in other mice until a gefitinib resistant tumor had been generated. The investigators then compared the resistant tumors to those tumors that were newly implanted and had not yet acquired resistance to the drug (gefitinib-sensitive). They found that a particular gene, EMP-1, was significantly expressed in the gefitinib-resistant tumors, whereas it was not expressed in the gefitinib-sensitive model.

“This tumor model was generated in such a way that it closely mimicked acquired resistance to gefitinib and EMP-1 was identified as a surface biomarker whose expression correlated with the development of resistance to gefitinib,” Agus said. “Molecular diagnostics, such as this, are extremely important as we attempt to personalize cancer treatments in the next decade.”

To confirm whether or not EMP-1 was present in patients with non small-cell lung cancer who were being treated with gefitinib in clinical trials, the investigators examined tumor samples from 39 patients. They found that none of the patients who responded to treatment with gefitinib expressed EMP-1. Alternatively, EMP-1 was present in 14 patients (28 percent) who had non small-cell lung cancer that had either stabilized or progressed. Importantly, however, one patient who initially did not express EMP-1 and had responded to treatment with gefitinib, later acquired resistance to the drug, and EMP-1 was significantly expressed when the cancer recurred.

“This tells us that the absence of EMP-1 does not completely predict whether a person won’t stop responding to gefitinib. However, it appears that testing for the presence of EMP-1 at the outset of treatment may help physicians predict which patients won’t benefit from the drug,” Jain explained. “Importantly, we found that EMP-1 is not only a marker for patients who won’t respond to gefitinib, but also for those who will later develop resistance to the drug.”

To confirm that EMP-1 was also present in patients with types of non small-cell lung cancer that do not respond to gefitinib, the investigators examined tumor samples from patients with adenocarcinoma and squamous cell carcinoma. They found that EMP-1 was expressed in 66 percent of the squamous cell carcinomas and 40.9 percent of those with adenocarcinoma, confirming that the presence of EMP-1 is directly linked to Iressa-resistance.

“This is an important new tool in the treatment of lung cancer which needs to be confirmed in ongoing large clinical trials,” said Ronald Natale, M.D., an oncologist at the Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute and a principal investigator on clinical trials with gefitinib, including the Iressa Dose Evaluation in Advanced Lung Cancer Trial 2 (IDEAL 2) that provided the basis for the initial approval of Iressa by the FDA.

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