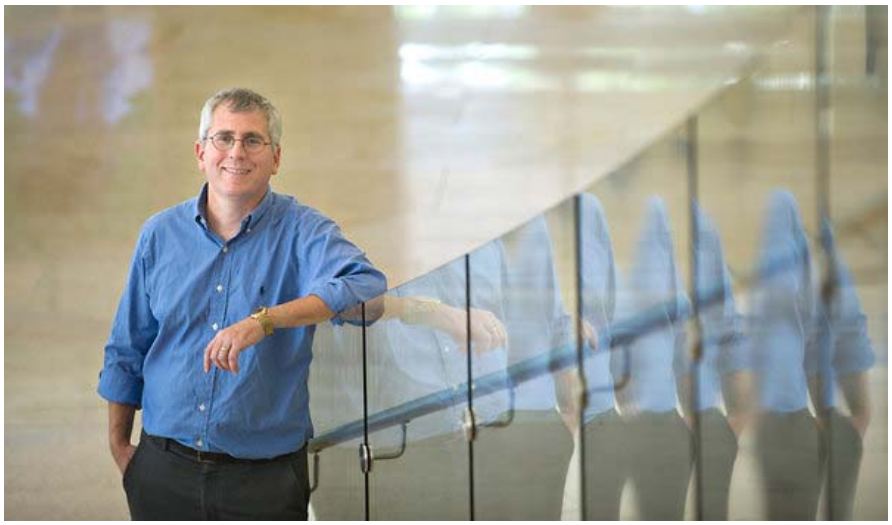
Cancer Study Points to Tighter Pairing of Drugs and Patients



Gretchen Ertl for The New York Times

Dr. Matthew Meyerson worked on a large study of squamous cell lung cancer. It found mutations that new drugs might target.

By GINA KOLATA
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The first large and comprehensive study of the genetics of a common lung cancer has found that more than half the tumors from that cancer have mutations that might be treated by new drugs that are already in the pipeline or that could be easily developed.

For the tens of thousands of Americans with that cancer — squamous cell lung cancer — the results are promising because they could foretell a new type of treatment in which drugs are tailored to match the genetic abnormality in each patient, researchers say.

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"This is a disease where there are no targeted therapies," said Dr. Matthew Meyerson of the Dana-Farber Cancer Institute in Boston, referring to modern drugs that attack genetic abnormalities. He is a lead author of a paper on the study, with more than 300 authors, which was published online in the journal Nature on Sunday.

"What we found will change the landscape for squamous cell carcinoma," Dr. Meyerson said. "I think it gives hope to patients."

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The study is part of the Cancer Genome Atlas, a large project by the National Institutes of Health to examine genetic abnormalities in cancer. The study of squamous cell lung cancer is the second genetic analysis of a common cancer, coming on the heels of a study of colon cancer.

The work became feasible only in the past few years because of enormous advances in DNA sequencing that allow researchers to scan all the DNA in a cell instead of looking at its 21,000 genes one at a time. The result has been a new comprehension of cancer as a genetic disease, defined by DNA alterations that drive a cancer cell's growth, instead of a disease of a particular tissue or organ, like a breast, the prostate or a lung.

And, in keeping with the genetic view of cancer, no one mutation in this study of squamous cell lung cancer stood out — different patients had different mutations.

As a result, the usual way of testing drugs by giving them to everyone with a particular type of cancer no longer makes sense. So researchers are planning a new type of testing program for squamous cell cancer that will match the major genetic abnormality in each patient with a drug designed to attack it, a harbinger of what many say will be the future of cancer research.

Squamous cell lung cancer kills about 50,000 Americans each year. That is more people than are killed in the nation by breast cancer, colon cancer or prostate cancer. Well over 90 percent of squamous cell cancer patients are or were smokers.

The new study compared tumor cells from 178 squamous cell lung cancer patients with the patients' normal cells. More than 60 percent of the tumors had alterations in genes used to make enzymes that are particularly vulnerable to the new crop of cancer drugs. Many of the drugs are already available or are being tested on other cancers.

These enzymes function like on-off switches for cell growth, said Dr. Roy S. Herbst of Yale Cancer Center, who was not an author of the new study. When they are mutated, the switches are stuck in an on position. About a dozen companies, Dr. Herbst added, have drugs that block these mutated enzymes.

Yet even though the squamous cell cancers analyzed in the study often had mutations in genes for these enzymes, the genes and the mutations were different in different patients.

"Unfortunately, what the Cancer Genome Atlas has revealed is that everyone's cancer could be very different," said Dr. William Pao, a lung cancer researcher at the Vanderbilt-Ingram Cancer Center in Nashville and an author of the new paper. "The field is really moving toward personalized medicine."

The study also found a real surprise, Dr. Meyerson said, something that had not previously been seen in any cancer. About 3 percent of the tumors had a gene mutation that might allow them to evade the immune system. By coincidence, an experimental drug that unleashes the immune system was recently tested in lung cancer patients. Some of those who did not respond might have the mutation, he said.

Now the challenge is to put the findings to clinical use.

First, researchers have to establish that the mutations in question actually are essential to the tumors' growth, said Dr. Bruce Evan Johnson, a lung cancer researcher at Dana-Farber and an author of the new paper. There are several steps: show that if the mutated gene is added to normal cells, they turn into cancerous cells; show that if the mutated gene is added to mice, they develop squamous cell lung cancer; and show that if the gene is turned off — with a drug, for example — in cells grown in a laboratory, the cells die.

Then come drug tests in patients. But if only a small percentage of patients have each of the mutations, that poses a problem. Ordinarily a few medical centers would enroll patients with a particular type of cancer, like squamous cell. But if, instead, squamous cell patients are subdivided according to their gene mutations, there would be too few for a

drug test within a single institution or even several.

So the plan is to cast a wider net. The major medical centers intend to form a consortium. In it, each center would direct one or more studies of one mutation and one drug that might home in on the specific mutation. So even though only a small percentage of squamous cell cancer patients would have that mutation, patients across the country could be in a clinical trial of a targeted drug. A patient's own doctor could administer the drug, and the medical center directing the trial could analyze the data in partnership with the company that makes the drug.

That sort of system worked for another common type of lung cancer, adenocarcinoma, Dr. Johnson said, allowing researchers to test drugs that work for only 2 to 3 percent of patients.

And the work can move fast, he added. A Pfizer drug, crizotinib, which targets a rearranged gene in some adenocarcinomas, entered clinical trials in 2008 for lung cancers with the rearrangement. The results were reported in 2009 and were published in 2010. Crizotinib was approved in 2011 for patients with the gene rearrangement. The rearrangement is so rare that about 1,500 patients were tested to find 82 whose cancer had it. They were the ones included in the study.

For Pfizer, the experience was transformative.

"The old way of doing clinical trials where patients are only tied together by the organ where their cancer originated, those days are passing," said Dr. Mace Rothenberg, senior vice president of Pfizer oncology.

Dr. Johnson, too, sees it as a wave of the future.

"That was the first time we really went after the genetic abnormality," he said.

Now, he said, with squamous cell cancer, "we are sort of where we were four or five years ago with adenocarcinoma."

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