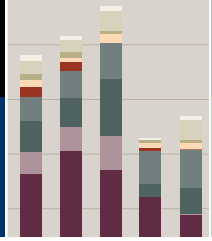
A boost for Germany
1373



No end to earmarks
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CANCER

First Pass at Cancer Genome Reveals Complex Landscape

Scientists have long known that the sparks that kindle cancer are mutations in a cell's genes. But most cancer-causing mutations have been discovered by looking in obvious places, such as in the genes that control cell division. Now it seems these efforts have barely glimpsed the big picture.

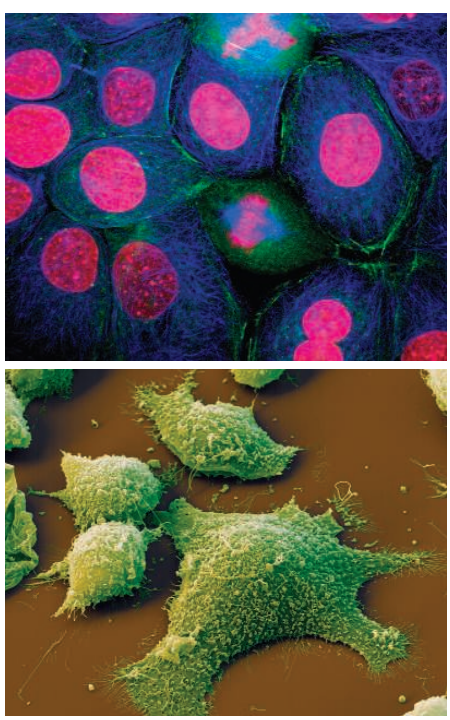
As reported online this week in *Science* (www.sciencemag.org/cgi/content/abstract/1133427), researchers have shined a searchlight across the genomes of breast and colorectal cancer cells, looking for mutations in more than half of all known human genes. And what they've uncovered is a much larger and richer set of cancer genes than expected.

The findings, hailed as a tour de force by other cancer scientists, should speed the race for new drugs, diagnostics, and a better understanding of tumor development. "It will take a long time to unravel all of this, but this is what cancer *is*," says Bert Vogelstein of Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland, a co-leader of the sequencing effort.

The results also appear to bolster The Cancer Genome Atlas, an ambitious $1.5 billion federal project to systematically search for genes mutated in dozens of cancer types (*Science*, 29 July 2005, p. 693). "I see this as a big shot in the arm for the argument that this strategy is going to work," says Francis Collins, director of the National Human Genome Research Institute in Bethesda, Maryland, which together with the National Cancer Institute (NHGRI) will soon announce details of a $100 million, 3-year pilot effort for the atlas. Adds Eric Lander, director of the Broad Institute in Cambridge, Massachusetts, who first proposed sequencing the cancer genome, "This is a beautiful demonstration that if you turn over every rock, there is a lot more to be found."

Yet even supporters of the atlas say this first, quick pass at describing all cancer mutations reveals daunting complexity. And not everyone has been convinced of the larger project's value. Geneticist Stephen Elledge of Harvard Medical School in Boston, while predicting that the new study will become a "classic paper," says that a costly sequencing project will give short shrift to functional genomics studies and take money away from investigators working on equally important cancer efforts. "I still believe we need a more balanced approach," says Elledge, who first expressed those concerns last year (*Science*, 21 October 2005, p. 439).

To conduct this mini–cancer-genome project, a 29-person team, headed by Vogelstein and Hopkins colleagues Kenneth Kinzler and Victor Velculescu, began with a database of 13,023 genes that are considered the best-studied and annotated of the 21,000 known genes in the human genome. Led by postdoc Tobias Sjöblom, the team resequenced the protein-coding regions of the genes in 11 breast cancer samples and 11 colon cancer samples, yielding 800,000-plus possible mutations. The team then winnowed out more than 99% of the mutations by removing errors, normal variants, and changes that didn't alter a protein.



Genetic bounty. Breast (*top*) and colorectal (*bottom*) cancer cells contain many mutated genes.

They ultimately found that the average breast or colon tumor has 93 mutated genes, and at least 11 are thought to be cancer-promoting. This yielded a total of 189 "candidate" cancer genes. Although some are familiar—the tumor-suppressor gene *p53*, for example—most had never been found mutated in cancer before. And the abundance of certain types of genes, such as those involved in cell adhesion and transcription, suggested that these processes play a huge role in cancer. The results, says Ronald DePinho of the Dana-Farber Cancer Institute in Boston, are a "treasure trove."

Verifying that each candidate gene is important to cancer won't be simple. Not only did the cancer genes differ between colon and breast cancers, but each tumor had a different pattern of mutations. The number of genes suggests that there may be more steps to cancer than thought. "It's a much more complex picture than we had anticipated," Vogelstein says.

At least two other pilot cancer-genome projects—one funded by NHGRI and one led by Michael Stratton and P. Andrew Futreal of the Sanger Institute in Hinxton, U.K.—are yielding similar results. The Sanger effort is looking at 500 genes in a larger number of tumor samples and cancer types and, according to an e-mail from Stratton and Futreal, has also found a "tremendous diversity of mutation number and pattern between cancers."

DePinho says the mutation differences from tumor to tumor could help explain why 90% of drugs fail in patients. Elledge, for his part, says the relatively small number of new genes common to the tumors reinforces his concerns about The Cancer Genome Atlas. He suggests that some of the government's money would be better spent on more direct studies, such as screens for lethal genes in cancer cells. The cost of the Hopkins study alone—Vogelstein says it took about $5 million, mostly from private funding sources—could fund five National Institutes of Health (NIH) grants on such topics, Elledge notes.

Despite such doubts, the atlas project gets under way next week. NIH will announce the three cancers to be studied in the pilot phase and a set of repositories that will supply tissue samples for sequencing. Centers that will characterize the genes will be announced in early October. The project is on an "extremely aggressive timeline," says DePinho, who co-chairs its advisory committee. **–JOCELYN KAISER**