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SPEEDY TECHNIQUE SHOWS WHEN GENES ARE TURNED ON

STANFORD — Scientists have developed a technique that can tell them at once which of thousands of genes present in a cell are switched on.

The method holds promise for medical diagnosis as well as for research into the workings of our cells.

"Researchers have done a great job of determining the sequences of a huge number of our genes. The problem is, we have the sequences of all these genes socked away in our data bases, but we don't know what they're there for, what the body wants to use them for," said Dr. Patrick O. Brown, a Howard Hughes Medical Institute assistant investigator at Stanford University School of Medicine.

"This technique will allow researchers to gather information about the genes' biology much more rapidly than with the traditional method," said Brown, who co-authored an article describing the technique in the Oct. 20 issue of the journal *Science*.

The article details an experiment focusing on gene expression in a common plant called *Arabidopsis thaliana* (mouse-ear cress). The Stanford researchers used the new technique to compare expression levels of genes in root tissues with genes in leaf tissues. Their results matched those obtained through the traditional method, called the northern blot.

Using the northern blot, a researcher spends several days to determine the expression level of a single gene. With the new method, the researcher could get the same information on more than 1,000 genes within the same amount of time – a process that would otherwise take months or years.

Here's how the new method works.

When a gene is expressed, or "turned on," the cell's machinery springs into action to create the specific protein encoded by that gene. This process depends on molecules called messenger RNA (mRNA), which carry the building instructions from each gene being expressed.

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Each gene creates a unique mRNA. The greater the amount of a particular mRNA in a cell sample, the greater the level of that gene's expression. The new technique measures the levels of particular mRNAs in cells.

The key to the technique's speediness is a robot designed to imprint small glass slides with arrays of up to 20,000 precisely placed microscopic dots of DNA samples. Each dot in the array carries a known DNA sequence corresponding to a particular gene.

After washing the array – called a "microarray" – with a fluorescently labeled mixture prepared from the mRNA of the cells under investigation, the Stanford researchers can tell which genes are being expressed and at what level. The brighter a dot glows, the higher that gene's level of expression.

The researchers speculate that the new technique will be adapted for clinical purposes, including disease diagnosis. For instance, Brown suggests using it to detect gene-expression changes in white blood cells – important players in our disease-defense system.

"White blood cells circulate through our bodies with little 'antennas' out, asking, 'How's everything going out there? Should we be kicking into gear to deal with a potentially threatening situation?' They have a sensing system that allows them to react to pathological conditions – and what they sense is reflected in gene expression," Brown said.

"If we can figure out how these changes in gene expression reflect the body's condition, we could use white blood cells as little spies wandering through the body and reporting back to us," he said.

Brown's co-authors were postdoctoral fellow Mark Schena, graduate student Dari Shalon and professor of biochemistry Ronald Davis. Shalon, who designed the robot that makes the microarrays, has launched a company (Synteni Inc., of Palo Alto, Calif.) to manufacture them.

The Stanford researchers, collaborating with a group at the National Institutes of Health, are now focusing on cancer genes. They are using the microarray technique on approximately 1,000 genes whose expression patterns are thought to reflect the progression of tumor development.

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