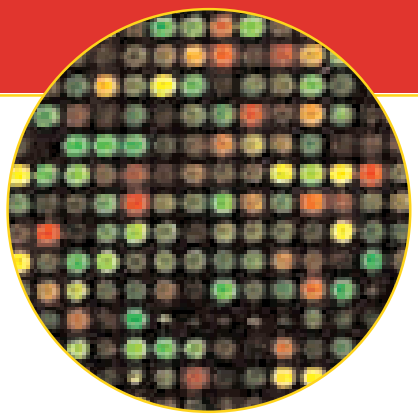
Modern Biology for High School Classrooms

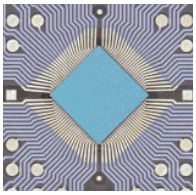
SNAPSHOTS of Science & Medicine

Volume 1, Number 2



DNA Chips

A Genetics Lab in the Palm of Your Hand



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Tools that speed access to information can be revolutionary. For example, computer modems have been sending data down telephone lines since 1962. But the wild, writhing mass we call the Internet couldn't really take off until computer modems could send text, pictures, and sound fast enough to keep the average Joe from falling asleep waiting. Who would surf the Web if each page took 20 minutes to load?

The DNA chip is a fast, new tool for acquiring information, and it promises to do for molecular biology what fast modems did for the Internet—namely, transform it from top to bottom. DNA chips, also known as DNA microarrays, are tools that will help scientists make sense of the huge mass of data flowing out of the human genome project and quickly get answers to questions they could only dream about a few years ago. You'll likely see them showing up in everyday life, too—in the doctor's office, for example, where they'll tell caregivers the specifics about each patient's genes, or in a police detective's standard toolkit, where they'll help convict the guilty and clear the innocent.

This issue of *Snapshots*, our second, tells you all you need to know about this powerful technology. **Research in the News** gives you an overview. The **Story of Discovery** tells you how DNA-chip technology developed. **People Doing Science** profiles a young scientist who's developing the commercial potential of microarrays at Genometrix, a Texas biotech company. **Social Impact** presents a fictional—but very possible—scenario from the world of crime fighting and asks you to think through how this technology should or should not be used. As always, we treasure your feedback. E-mail us at **Robert.Taylor@od.nih.gov**, or hit the "Contact Us" button on the Web site.

Robert Taylor, Ph.D.
Editor, *Snapshots of Science & Medicine*

RESEARCH IN THE NEWS

A Genetics Lab in the Palm of Your Hand

by Ivan Amato

Once you get past kindergarten, the alphabet is pretty much old hat. Yet we use this little set of symbols to express lifetimes of thoughts, jokes, dreams, and joys. Shakespeare's plays, Sweet Valley High novels, the U.S. Constitution, comic books—all written with the same set of squiggly lines. Pretty amazing. But unless you know how letters work together to form words, sentences, and ideas, Shakespeare looks a lot like Sweet Valley—just gobbledygook.

Living things have a language, too, coded in the order of the nucleotide letters A, C, T, and G in their genes. One of the great scientific quests of the past—that's the 20th—century was to understand this "language of life." First, scientists learned that cells store their instructions for living in their DNA. Then, researchers figured out how cells convert the nucleotide sequences in DNA into the sequences of amino acids that make up proteins. Now, scientists are busy reading out complete DNA sequences for whole organisms. They already have a rough draft of virtually the entire human genome, all 3 billion nucleotides of it.

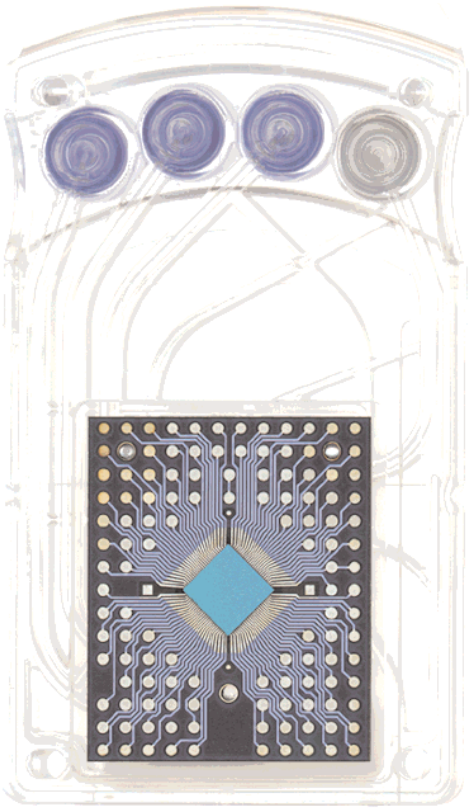
Unfortunately, a genome's worth of raw sequence data is about as comprehensible as a shredded encyclopedia. You might pick out individual words, or even a few paragraphs, but you still can't readily understand how the whole thing fits together.

In the 1990s, scientists developed a new tool for deciphering DNA called a "DNA chip," also known as a "DNA microarray." It allows one scientist to collect more information about DNA sequences in an afternoon than an army of scientists could collect in several years using earlier techniques.

DNA chips promise to carry the science of understanding genomes to a whole new level, and to bring tools for getting DNA-sequence information out of research labs into doctors' offices, the better to tailor-fit medical treatments to an individual's particular genetic makeup.

In fact, says Leroy Hood, a molecular biologist at the University of Washington in Seattle, DNA-chip technology will be key to meeting one of the biggest scientific challenges of the coming century—the analysis of how all the genes in an organism work together as a very complex system.

The brain has about a trillion neurons, and about a quadrillion interconnections, says Hood. What we call "consciousness" somehow "emerges" from how all these neurons interact. "We could study an individual neuron for 50 years, and that wouldn't tell us one iota more about the brain's emergent properties, because they arise from the network, not a single cell," says Hood. "If we were to study each gene in isolation, we'd never know how the genome functions as a whole. DNA chips are the prototype global technology for genetics, because they let us look at the behavior of thousands of genes at once."



A hand-held DNA chip and sample-handler, made by Nanogen, Inc. The sample ports are at the top, and the chip is the blue diamond in the center.

How Chips Work

DNA chips come in many varieties. Some are "homemade" in scientists' laboratories, with glass microscope slides and a robot arm wielding a high-tech fountain pen. Private companies are developing other techniques for mass production. But DNA chips all depend on the same basic principle: Complementary DNA stands stick together.

First, recall that a double-stranded

DNA molecule can unzip into two complementary strands. Each of these can zip back together with its complementary sequence. That could be either its old partner, or a new partner with the same sequence. The trick that makes DNA chips work is that you can tether a "new partner" to a flat surface.

Imagine a standard checkerboard, 8 squares on a side, 64 squares total. In each square, you tie down a different snippet of single-stranded DNA just three nucleotides long. You write down the sequence in each square. (You can make 64 different sequence variations from three nucleotides—ACG, CGT, GTA, TAC, AAA, and so on—so there's just enough room for all the possibilities.)

Now imagine you have an unknown sequence, also three nucleotides long. To find out what this unknown is, set it loose on the array so that it wanders from square to square. When your unknown sequence finds its complement, it sticks. To figure out your unknown sequence, all you have to do is find which square your unknown DNA stuck to. Because you know the sequence of the DNA you tied down to that square, you know that the unknown sequence is the complement. (See illustration below.)

Using Chips

What gives DNA chips their power in the real world is their flexibility, compact size, speed, and low cost. Scientists can put not just a hundred but hundreds of thousands of distinct DNA sequences on a microscopic grid a few centimeters across. Then, using fluorescent molecular tags that light up when a complementary strand binds to a particular spot, a person (or a robot) can read out which sequences on the chip find their complement in an unknown sample.

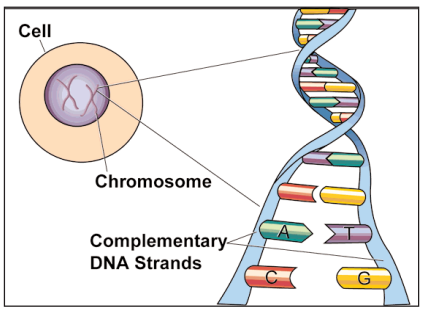
DNA chips can gather an incredible variety of data very quickly. And because chips can be mass-produced, they will likely be very inexpensive in the near future. That will allow easy collection of genetic information from many, many individuals, opening up all kinds of opportunities to help doctors diagnose and treat their patients.

Expression Analysis

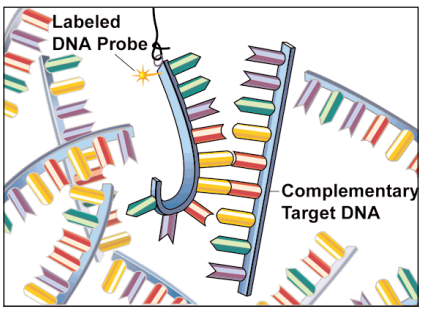
One way DNA chips allow scientists to observe genes working together is called "expression analysis." (Remember that to "express" a gene as a protein, cells first transcribe the gene's DNA sequence into a complementary mRNA copy. Then a ribosome translates the mRNA sequence into the string of amino acids that makes up the protein. Cells constantly switch genes on or off as conditions change. To understand a cell's behavior in response to a stimulus—the presence of a hormone, say, or a toxin, or some environmental signal—it would be handy to have a minute-to-minute reading of which genes are turned on.

"We could study an individual neuron for 50 years, and that wouldn't tell us one iota more about the brain's emergent properties, because they arise from the network, not a single cell," says Hood.

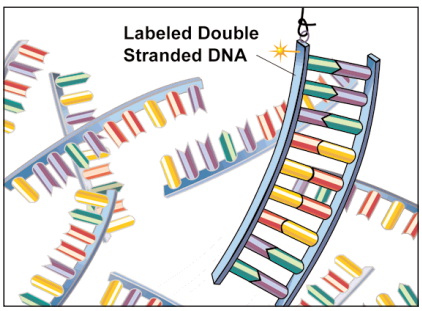
DNA chips are just about perfect for tracking this kind of minute-to-minute change in gene expression. For example, Patrick Brown and his colleagues at Stanford University wanted to find out the details of how yeast cells make spores. Other scientists had already determined the DNA sequence



Cellular DNA is double-stranded. Chromosomes in a cell's nucleus contain double-stranded DNA. The bases in the two strands are complementary—A is opposite T, C is opposite G.



Using a single probe. In the 1970s, scientists learned to use DNA probes to find specific target sequences in solution. First, they radioactively label a known DNA sequence, then they put it into a mix of unknown sequences. If the probe's complement is there, it will bind.



Look for the label. Next, separate the double stranded DNA from the single stranded. If the probe found its target, the radioactive label will be in the double stranded fraction.

of every possible mRNA a yeast cell makes. So, Brown and his colleagues put the complements of each of these possible mRNA sequences onto a chip. Then, they ground up a bunch of resting yeast cells, which of course contained an mRNA corresponding to each gene that was active the moment the cells hit the blender. Next, the researchers spread this mixture over the surface of the chip. Only the spots corresponding to genes that were actively churning out their mRNA lit up, because these were the only spots on the chip that had found their complementary sequence.

This first experiment gave Brown and his colleagues a baseline. Next, they stimulated the yeast to form spores (by taking away their food) and repeated their chip analysis six times over the next 12 hours. By looking at which genes turned on, and when, Brown and his colleagues got many new insights into how yeast cells genetically shift gears to make spores.

But the significance of Brown and company's work goes way beyond yeast physiology—it paved the way for using DNA chips to see how dozens of genes work in concert to change a cell's behavior.

Expression analysis has medical applications, too. For example, a team led by Eric Lander, director of the Whitehead Institute at the Massachusetts Institute of Technology, announced last October that they used expression analysis—made possible by a DNA chip—to develop a test to classify different types of leukemia. (To choose the best treatment, doctors need to know exactly what type of cancer a patient has.) These researchers looked at samples from about 50 patients already known to have one of two different kinds of leukemia. Then, using the patterns of gene expression they found in the two groups, they correctly predicted which type of leukemia several patients had. In the near future, doctors may be able to use this test to decide which is the best treatment for a new leukemia patient. Researchers also plan to develop similar tests to match treatments to patients for other kinds of cancer, too.

Mapping Our Differences

Pick any two people in the world, and you would find their DNA is 99.9 percent identical. The remaining 0.1 percent is the genetic basis of all of humanity's differences, from the shape of our faces to the way some patients respond to a certain drug while others don't. Scientists are now starting to use DNA chips to map out tiny one-letter variations in the 3-billion-nucleotide human genome. These pinpoint differences are called "single nucleotide polymorphisms," or SNPs. Identifying them will help researchers understand the basis for human variation.

But to map SNPs, you need a different kind of chip. For expression analysis, you use a chip containing all possible genes. For SNP work, you make a chip with many, many possible variations of one gene. Then you take a DNA sample from the person you want to test, use PCR to make multiple copies of the gene you're interested in, and put this "amplified" sample on the chip. The spot that lights up will correspond to the particular sequence variant the person has. Because the test is quick and not too expensive, you can do many of them. Then, you correlate different outcomes—response to a certain drug, for example, or the probability of getting heart disease—with the different genetic variations.

Francis Collins, director of the National Human Genome Research Institute in Bethesda, Maryland, is enthusiastic about SNP analysis. "There are only about 200,000 functionally important variants [SNPs] in the human genome that have reasonable frequencies," he says. "Nearly all of the genetic contributions to diabetes and heart disease

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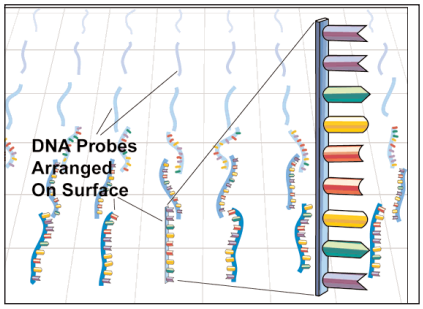
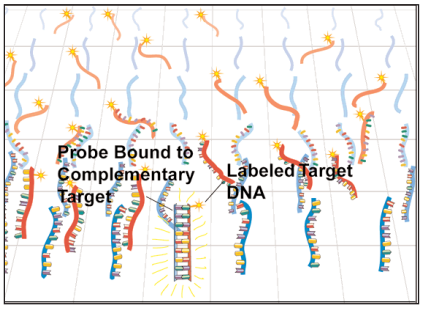
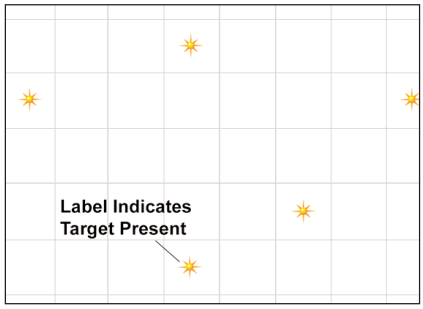


DNA Chips: Thousands of Probes at Once. DNA chips allow scientist to use thousands of probes all at once. First, they spot the different probes on a flat surface, often glass. They keep a record of the sequence they put at each spot.



Let the Targets Loose. With chips, scientists label the targets in solution and put the solution on the chip. Any targets that find their complementary probes will stick to the surface.



Look for the Label. Next, they gently wash the surface, and look for the labeled spots. Because they know the sequences of all the probes, researchers can easily deduce the sequences present in the solution.

STORIES OF DISCOVERY

Molecular Biology Meets the Microchip

by Karen Hopkin, Ph.D.

It's the spring of 2020, and your grades have taken a nose dive. You just can't seem to concentrate on the books—at home, your kid sister is driving you nuts, and at school, you're having serious daydreams about your lab partner. So when your mom throws a fit about your "poor academic performance," she drags you down to the doctor for a DNA check. One drop of blood, and five minutes later, the results are in: Your door-slamming, eye-rolling, class-cutting, and body-piercing genes are all turned on; your yessir-ing, exam-acing, supper-table-clearing, and get-to-bed-by-8:30 genes are completely shut down. Diagnosis: puberty.

DNA chips stand to help us understand, at the most fundamental level, how cells work.

Okay, so that's a bit far-fetched—body piercing is probably controlled by a whole bunch of genes. But the idea that you can learn everything about anybody's genetic makeup quickly and easily is fast becoming a reality, thanks to DNA chips.

These chips, also known as DNA microarrays, are made of a silicon or glass plate studded with DNA fragments. Smaller than a postage stamp, DNA chips will someday make it possible to identify and analyze every one of your genes in an afternoon. A trip to the doctor's office, for example, may involve a quick check of a few critical genes to determine whether you'll react well or poorly to a drug, which kind of bug you've caught, or whether you're likely to develop heart disease, cancer, or Alzheimer's.

These powerful gene screens spring from the marriage of two technologies: techniques for slicing, dicing, and sequencing DNA and the miniaturization that reduced 30-ton mainframe computers to something you can carry in one hand. DNA chips come in a variety of flavors, with different substrates, different DNAs, different methods of preparation. But they all exploit the fact that every single strand of DNA will bind tightly to its perfect partner, its complementary strand. So DNA fragments anchored to a chip will latch onto their partners if the partners are present in a solution sloshed over the chip surface. Because you know the sequence of DNA stuck to the chip at each particular spot, you know that the sequence that will stick to that spot (see Research in the News for details).

Gregor Mendel

In some sense, we are our genes. By offering a way to examine our genes—and the genes of other organisms—DNA chips stand to help us understand, at the most fundamental level, how cells work. And what it is that makes you, well, you. Which is remarkable, considering that 50 years ago, scientists had no idea what DNA even looked like, much less how it worked.

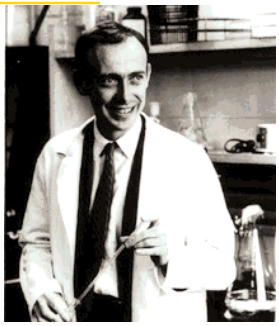
To follow the twisty, turny pathway that led to DNA chips, wind your way through this timeline.

1865 Gregor Mendel, a curious Austrian monk, publishes a study showing how living things—he was working with pea plants at the time—inherit physical characteristics from their parents and pass them along to their offspring. Cross short plants with short plants, for example, and the resulting crop will be (you guessed it) short. By crunching the numbers from many, many plant matings, Mendel realizes that individual traits are inherited separately—a tall plant can have green peas or yellow peas, just as a tall person can have brown eyes or blue. Incidentally, scientists believe that Brother Gregor—though he really did unravel the laws of inheritance—may have fudged his data a bit to make the pattern he found "cleaner." In real life, data never come out that good.

1909 Danish biologist Wilhelm Johannsen names the "units of inheritance" described by Mendel's genes. Nobody yet knows what these so-called genes are made of.

1944 Oswald Avery, Colin MacLeod, and Maclyn McCarty of Rockefeller University in New York City prove that genes are made of DNA and that DNA carries and transmits genetic information from cell to cell, generation to generation.

1953 James Watson and Francis Crick determine the molecular structure of DNA. Two strands of DNA wind around one another in a double helix. The nucleotide bases—A, T, G, and C—run down the center of the helix, the A from one strand always pairing with a T on the other; the Gs pairing with Cs. This arrangement—the pairing of complementary bases—allows DNA to be copied. It also allows the pairing of matching sequences on DNA chips. In 1962, Watson and Crick take home a Nobel prize for their efforts.



James Watson

1959 In the seemingly unrelated world of computer electronics, Robert Noyce and Jack Kilby first use a process called photolithography to build integrated circuits—tiny transistors, capacitors, resistors, and diodes—onto silicon chips. These miniature circuits allowed computers to shrink in size. Decades later, molecular biologists adopt this technique for building nucleotide arrays onto DNA chips.

1960 Molecular biologist Julius Marmur and others realize that a little heat causes double-stranded DNA to melt into two strands, which reconnect with their partners when cooled back down.

1965 Scientists first propose that when fishing for DNA matches, attaching the bait to a solid support should make it easier to detect complementary sequences.

1975 Biologist Ed Southern popularizes a method for cutting DNA into manageable bits, arranging these fragments in size order and securing them to a piece of filter paper. In this method, called Southern blotting, radioactively labeled pieces of DNA are washed over this DNA-coated filter, and fragments with complementary sequences stick to their partners on the paper. Exposing the filter to X-ray film (to locate the radioactive labels) allows researchers to identify which sequences match. Molecular biologists use a similar technique for identifying matching RNA sequences. As a pun, they call the method "Northern" blotting. The name sticks.

1977 Molecular biologists Fred Sanger and Walter Gilbert come up with related methods for chemically sequencing DNA—reading the nucleotide bases that make up genes one letter at a time. The techniques are used today for scanning the genetic blueprints of life. In 1980, they win a Nobel prize for their work.

1979 Researchers develop a shortcut to Southern blotting. Instead of separating DNA by size, biologists simply plop mixtures of DNA onto filter paper in big dots. These "dot blots," like their Southern cousins, are then probed for matches with radioactively labeled DNA fragments. (Dot blots that contain DNA samples taken from different organisms are affectionately dubbed "zoo blots.") DNA chips are essentially dot blots in which samples are spotted onto glass slides rather than filter paper.

1985 Kary Mullis describes the polymerase chain reaction, or PCR—a technique that allows researchers to make millions of copies of any piece of DNA they wish to study. The method is used for generating the DNA fragments for chips and has proven indispensable for almost all the genetic studies done today, including large-scale DNA sequencing of organisms from yeast to humans. Mullis, who claims that the idea for PCR came to him while he was cruising in his Honda Civic along the California coast, is awarded a Nobel prize in 1993.

Around the same time, researchers come up with a means of tagging DNA nucleotide bases with a fluorescent dye. The trick makes sequencing DNA simpler and paves the way for using fluorescently tagged DNA to detect complementary sequences on gene chips.

1989 Congress launches the Human Genome Project, awarding $3 billion in funds for a 15-year effort to determine the exact sequence of the 3 billion DNA bases that make us human. And to compare the human genome with the DNA sequences of mice, yeast, fruit flies, and other model organisms. A decade later, researchers around the world celebrate sequencing the one-billionth base of human DNA.

1991 Scientists at the California-based biotech company Affymax produce the first DNA chips. Affymax takes advantage of photolithographic techniques similar to those used to etch circuits onto computer chips to build their DNA probes, base by base, onto a silicon wafer or glass slide. By selectively covering and exposing the growing stacks of nucleotide bases,

Kary Mullis says his Nobel prize-winning idea for PCR came to him while driving along the California coast.

the scientists can control what sequences they lay down on the array. Researchers then flood this chip with fluorescently tagged DNA—isolated from a bacterium or from your blood, for example—and look to see which sequences stick. Because they know the exact sequences of the DNA probes on the grid, the researchers automatically know the sequences of the fluorescent fragments bound to them. DNA that doesn't find its match on the chip is simply washed away.

Affymetrix, a spinoff company dedicated to gene-chip technology, is established in 1993. Today the company offers a variety of gene chips, including human DNA arrays and chips for identifying HIV strains or detecting mutations in cancer genes. The chips are dense, sporting up to 400,000 different DNA probes in an area the size of a thumbnail. But their price tag—up to $2,000 per single-use chip—puts these arrays out of the reach of many basic researchers.

1995 Researchers at Stanford University, led by Pat Brown and Ron Davis, work out a recipe for making DNA chips right in the laboratory. Instead of building the probes one nucleotide at a time on a silicon surface, à la Affymetrix, these researchers spot whole DNA fragments onto a glass microscope slide. To make their arrays, Brown and his colleagues build a robot that uses fountain pen–like tips to dot tiny droplets of a solution containing the DNA probes—large pieces of genes copied by PCR—onto the slide. These DNA chips are like the dot blots developed in the '70s, only better: They're more sensitive, they require less sample DNA, they don't rely on radioactivity, and you can do tens of thousands of blots in a single run. Once a lab is geared for production, Brown estimates, chips will cost about $20 apiece. His Stanford Web site offers complete instructions for any lab interested in do-it-yourself DNA chips, making the technology accessible to the scientific community.

1996 Researchers start putting DNA chips to the test. In 1996, Francis Collins of the National Human Genome Research Institute in Bethesda, Maryland, uses an Affymetrix microarray to detect mutations in the breast cancer gene *BRCA1* in women at risk for the disease. Within a year, Brown and his colleagues synthesize the first chip containing all 6,000 yeast genes. The chip enables researchers to track which genes are switched on (or off) as yeast cells grow, divide, form spores, or defend themselves against poisons. For the first time, researchers are seeing global "gene-expression patterns," with whole clusters of genes turning on and off together to orchestrate the activities of a living organism.

1998 Researchers begin to use DNA chips to identify and catalogue polymorphisms—single-nucleotide-base changes that may affect whether a patient will respond to certain drug treatments.

1999 DNA chips prove valuable for classifying and studying cancers. Researchers at the Whitehead Institute at the Massachusetts Institute of Technology (MIT) and others at Stanford find that by examining gene-expression profiles, they can differentiate between two different subgroups of leukemia. Only one subtype offers a good chance of survival. These results suggest that gene-expression profiling with DNA chips may be useful for diagnosing, and perhaps treating, leukemia.

In other labs, DNA chips allow researchers to examine everything from which genes make strawberries ripen to which genes make the Ebola virus so deadly. In October, young scientists anxious to take advantage of DNA-chip technology pack a course at Cold Spring Harbor Laboratory in New York in the hopes of learning how to build the robots they need to break into the chip biz. A handful pony up $30,000 so they can take the equipment home after class.

Tomorrow Analysts estimate that the market for DNA microarrays will be $500 million to $1 billion per year, so, clearly, chips are in demand. In the future, advances in technology should make DNA chips cheaper and easier to make. Several groups of researchers, for example, are developing methods for printing chips using devices similar to an ink-jet printer. Eventually, custom-order chips may be commercially available, just a mouse click away. In the meantime, molecular biologists have teamed up with computer scientists and programmers to devise ways to make chips easier to read, and the resulting data easier to analyze. Soon scientists will have access to DNA chips containing every gene in mice or humans. With chips in hand, we'll be that much closer to the dream of understanding ourselves—down to the very last base. •

RESEARCH IN THE NEWS

Molecular Biology Meets the Microchip

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and hypertension and all of the common illnesses are found in those 200,000 elements." Moreover, says Collins, once researchers know which SNPs correlate with higher risk for disease, people with these traits will be able to take extra steps to avoid getting sick. This might allow "medicine to move from its present mode, where we spend most of our resources treating people who are sick, to a preventive strategy, which is individualized," says Collins.

Big Power, Big Responsibility

DNA chips will help scientists make sense of genetic information. Medical applications are on most people's minds, but the same technologies can be used for everything from confirming lineages of racehorses to teasing out evolutionary relationships between closely related species.

But as the power of chips and genetic science grows, questions that society must answer pop up right and left. Should employers use genetic information in hiring decisions? How about insurers who may want to avoid insuring people at high risk for certain diseases? How about a zealous political group trying, say, to portray an opposing candidate as having a high risk of dying of a heart attack? Today, it's impossible even to list all the questions, let alone answer them. (Do the Social Impact section, for insight into one interesting question.) It will take laws, regulations, restraint, and wisdom to ensure that the good consequences of the genetic revolution outweigh the bad, say many researchers, including Lander. "I know of no other field that is more exciting, or in which it is more important for us all to imagine the future," he says. •

On the Web

If you only have the print version of *Snapshots of Science & Medicine*, you don't have it all. Come to our Web site (http://science-education.nih.gov/snapshots) for more. For the DNA chips issue, we have

- All the articles you see here, but in **flashy color** and optimized for the Web.
- **Audio versions** of all our articles. Eyes tired? We'll read to you.
- A **Shockwave animation** explaining how DNA chips work.
- Hands-on **classroom activities**, complete with good graphics and a teacher's guide, to help students really get a grip on the science behind this technology.
- • A compendium of further **Web resources** about DNA chips.
- All the **past issues** of *Snapshots*.
- A **feedback page**. We really, truly want to know what you think of our publication and any ideas you have for making it better.

PEOPLE DOING SCIENCE

Archana Nair: DNA Microarrays on an Industrial Scale

by Richard Currey

Archana Nair

By her own admission, Archana Nair is a little bit impatient. "I'm always eager to see results in final form," she says, "and I like to get things done." Fortunately, this approach is exactly what she needs in her work at Genometrix Incorporated, a young biotech company near Houston, Texas. At Genometrix, Archana is helping develop a powerful new technology, variously known as DNA chips, DNA arrays, or DNA microarrays.

A fusion of computer science, bioengineering, and genetics, DNA microarrays are small plates spotted with hundreds to thousands of specific DNA sequences from plant, animal, or human tissues (see Research In The News for details). Far superior to older techniques that could study only one gene at a time, DNA arrays can tell researchers about the activity and sequence of many genes in a test sample with a single, short procedure.

Archana's path to Texas began on the other side of the globe. She was born in Bombay, India, and raised in New Delhi, where her father worked in the plastics industry and her mother taught grade-school math and science. In high school, Archana found she had a real affinity for science—especially biology. "My first high-school biology teacher, Bimala Ghai, taught me the significance of understanding the science, as opposed to rote learning," Archana recalls. "She helped me see that science is a creative activity, with so much still to learn and explore. I was excited by the sheer scope of the subject, by all the ways that science touches everything we do."

Her high-school science experience inspired Archana to pursue biology as a career. After graduating with a B.S. in Botany from Delhi University, she went on to earn a master's degree at the Indian Institute of Technology, in Kharagpur, specializing in molecular genetics and biochemistry. She returned to New Delhi to begin her professional life, taking a job with the Tata Energy Research Institute. There, she carried out experiments aimed at developing more-productive strains of plants.

"I was fortunate enough to learn a lot of the how in India, but I didn't know the why. To grow and develop as a scientist, I needed the why. And that's what brought me to the United States."

This job was something of a turning point, Archana says, because it introduced her to applied molecular genetics, the science of manipulating and copying genes. "I knew then that molecular genetics was the future of biology—and my future," she says.

But that meant moving on. In India, "we didn't have any schools where I could get a degree in molecular biology that I could then apply right away, and I was in a hurry to work sooner rather than later," Archana recalls. Moreover, she adds, "I was fortunate

Just because you work hard doesn't mean you don't get around. Archana sightseeing in Alaska.

enough to learn a lot of the how in India, but I didn't know the why. To grow and develop as a scientist, I needed the why. And that's what brought me to the United States."

Archana vacationing in Yosemite National Park.

She found her way to the University of Florida, where she earned a second master's degree, this time in molecular and cell biology. She then worked with microarray technology for three years at another biotech company before joining Genometrix in 1999. Genometrix was founded in 1993 to develop DNA-chip technology. The company makes and analyzes customized DNA microarrays for researchers in universities and the pharmaceutical industry, helping speed up drug discovery and basic biological research.

When she first joined Genometrix, Archana helped set up the processes and procedures the company uses to deliver the information its customers need. In her current position as a group leader in the Process Engineering Team, she troubleshoots any issues that come up on the production floor. That includes implementing long-term improvements in automated procedures, as well as dealing with all the little glitches that inevitably crop up. "This means I'm always interacting with the different engineers and scientists who handle automation, bioinformatics, and research and development, as well as those who operate the equipment and do the analyses," says Archana.

"For me, the challenges and potential in microarray technology make a thrilling blend of molecular genetics and computer science."

The variety and hectic pace of her everyday work always hold her interest, but she also likes being right on the cutting edge of biotechnology. "Microarrays are the doorway to future biological research—in preventive health, medical diagnostics, and the development of new medicines, to name only a few applications," she says. "I like to think of the difference between conventional gene techniques and microarrays as analogous to the difference between ground-based telescopes and the Hubble space telescope. The older techniques work, but the newer ones allow us to 'see' better and farther.

Archana as a young student in India.

"For me," Archana continues, "the challenges and potential in microarray technology make a thrilling blend of molecular genetics and computer science. The whole field of bioinformatics [using microarrays to find patterns within large volumes of DNA data] is limited only by our imagination. Think about it: We can now simultaneously target multiple specific genes, and see how they react to or interact with other genes, or to external variables such as drugs, bacteria, or viruses. We can look for correlations, connections, or relationships—some of which will inevitably be very surprising! This entire area of research will grow by leaps and bounds. And I want to grow with it."

As DNA microarrays accelerate the pace of discovery, Archana foresees new breakthroughs in scientific research that will prompt fundamental revisions in the prevailing theories of life, heredity, health, and disease. And—in character—she's in a hurry to get there. "I'd love to leap forward 50 years and see the changes wrought by microarray technology," Archana says. "I guarantee those changes will be remarkable." •

SOCIAL IMPACT

DNA Dragnets: How Much Testing is Too Much?

by Ronnie Yashon, Ph.D., J.D.

The Social Impact section is your opportunity to work through an ethical, legal, or social question that the research we're reporting on has raised. Many times, these questions are so new, it's difficult to pose them clearly, much less answer them easily. For this issue of *Snapshots*, the question is, How broadly should police be allowed to cast a "DNA dragnet" while investigating a crime? As the cost of doing DNA-identification analysis comes down and the speed increases, interest in using this technology to sift through large groups of people in a search for suspects will surely grow.

First, students should read the scenario below. Then, they should pick a question from the list and work through the Decision Form on the next page. The form is designed to mimic the kind of back-and-forth discussion the society at large will go through as people attempt to reach consensus on this and other questions that biomedical research raises.

Scenario*

September 9, 2003. Peyton County Police Detective John Franklin has a very hard case on his hands. Two women, Mary Adams, age 24, and her sister Gloria Adams, age 17, were brutally murdered while camping near Yorktown Springs, a small town in his jurisdiction. The crime occurred at night in Big River State Park, during a heavy rain. Franklin can find no witnesses, no footprints, no murder weapon, no tire tracks, and no fingerprints. He has only one good lead—bits of skin under the fingernails of Gloria Adams, almost certainly from the killer. A DNA match to this tissue would conclusively link a suspect to the crime.

But where should Detective Franklin start? He has no suspects. However, just last week a company called Gene Identification Systems sent him a brochure about a new product. It uses a device called a DNA microarray to do DNA-identification analysis very quickly and for relatively little money.

* *NOTE: This scenario is fiction. Any resemblance to real people, events, or places is purely coincidental.*

Because Yorktown Springs is so small, Franklin thinks he could use the new technology to carry out a "DNA dragnet." He could ask all 2,143 adult residents to give a DNA sample—just a Q-tip rubbed gently inside the cheek—and test them all. With Gene Identification's microarray technology, he could do all the testing for less than $20,000, and get the results in just 3 days. DNA dragnets have been used frequently in Great Britain, and they sometimes get results.

Franklin decides to try. He makes a list of all the people in the county over age 17. He contacts them all, and asks each to provide a sample voluntarily.

Questions

1. **Imagine you live in Yorktown Springs and Franklin asks you for a sample. What would you do?**

2. **After Detective Franklin sends out a letter to all adults in the area, he begins testing. The 238th person on the list, a man named Irving Tomston, doesn't respond to letters or phone calls. What should Franklin do?**

3. **After processing samples from all Yorktown Springs residents over 17 years of age, Franklin doesn't find a match. What should he do?**

4. **A match is found in the samples taken in the dragnet. At trial, the defense argues that the evidence should not be admitted. What should the judge do?**

5. **After the testing, Franklin announces that his department will put all the DNA profiles collected in the dragnet into a computer database for future investigations. Should he be allowed to do this?**

Policemen conduct a DNA dragnet in the town of Wee Waa, in New South Wales, Australia. (See "A Few Fast Facts About DNA Dragnets," page 14.)

SOCIAL IMPACT

Decision Form

Student's names

Which question on page 12 will you or your group address? _____

List three possible answers to this question.

1.

2.

3.

Come to a decision about which of these answers is best, and circle that number.
List three reasons why this is the best answer.

1.

2.

3.

List three reasons other people might not agree with your best answer.

1.

2.

3.

With those counter arguments in mind, why is your answer still the best?

Identify at least three people or groups with a stake in the question, and state how they would be affected by your solution.

1.

2.

3.

Give two possible outcomes for the country if your solution was put into practice.

1.

2.

SOCIAL IMPACT

A Few Fast Facts about DNA Dragnets

- Although the scenario presented here is fictional, DNA dragnets have been employed in other countries, including the United Kingdom and Australia. For example, on January 1, 1999, a 91-year-old woman was raped in her home in Wee Waa, a small town in New South Wales, Australia. The police had no good leads. In April 2000, police asked all men between the ages of 18 and 45 living in and around the town to give a saliva sample for testing. Stephen Boney, a 44-year-old laborer, was one of over 600 men who gave a sample. Ten days later, before his sample was analyzed, Boney confessed to the crime. He pleaded guilty at his trial on July 11, 2000, and now awaits sentencing.

- Taking DNA samples from many people in a specific area is called a mass DNA screening or a "DNA dragnet." As the cost of doing DNA analysis comes down, interest in this tactic will surely grow.

- Currently, DNA identification is labor intensive and costs about $50 per sample. DNA microarrays could dramatically reduce this cost, however, making it more practical to test a lot of people quickly.

- DNA-identification analysis reveals nothing about any physical traits a person might have. It's useful for identification only.

- To do DNA identification, labs analyze a set of DNA sequences called short tandem repeats (STRs). As the investigator analyzes more STRs, the chance of a random match goes down. The FBI has identified a standard set of 13 STRs for DNA identification. The chance that two people are identical in each of these 13 STRs is virtually zero.

- DNA testing could conceivably reveal much about person's physical characteristics. If the original sample is also kept, not just the identification profile, an enormous amount of information about an individual's genetic traits could be acquired by performing other tests.

Next Time in SNAPSHOTS...

RESEARCH IN THE NEWS

"A banana a day keeps the doctor away." Researchers at the Boyce Thompson Institute (BTI) are busy adding bits of bacterial and viral DNA to bananas, potatoes, and other food plants to create "edible vaccines." By serving up the antigens that the inserted DNA sequences encode, the researchers hope to give people long-lasting immunity. If it works, the fruits could provide a powerful and relatively inexpensive way to fight disease—especially in poor countries, where a single dose of a standard vaccine can cost many times the average amount a person there spends in a year for all health-care needs combined.

STORIES OF DISCOVERY

The idea of making an edible vaccine is the result of blending two fields that you might not think would ever belong together—namely, human immunology and plant biotechnology. Find out how these two different parts of science grew up and, eventually, grew together.

SOCIAL IMPACT

The need for new ways to prevent disease, especially in poor countries, is clear. But the whole idea of genetically modifying foods has caused a worldwide uproar. This section allows you to explore how these two issues together might play out when it comes to genetically engineering fruit to prevent illness.

PEOPLE DOING SCIENCE

Joyce Van Eck spends much of her time trying to make plants make mistakes. Specifically, Van Eck, director of the Plant Transformation Facility at BTI, develops new ways to mass-produce mutant plants. By looking at what physical and chemical changes the mutations cause, researchers can better understand what each plant gene does. **Sarah Abend** is a research assistant who works with Van Eck. Abend earned a bachelor's degree in plant science in 1997, and figures that's enough formal schooling for her. She plans a career in industry, working on applications of plant engineering.

Summary Guide: DNA Chips

Here are some basic facts about DNA chips. Don't memorize this list, but read through it. After reading this issue of *Snapshots*, you will (we hope) be able to say, "OK, I knew that," about each point.

- DNA chip is slang for DNA microarray.
- DNA chips are a revolutionary technology. They speed up research, helping scientists understand the primary sequence of the human genome, now almost complete. They will also allow doctors to get important genetic information from individual patients and, therefore, to choose the best treatments.
- Each of the strands in a bit of double-stranded DNA is complementary to the other. Adenine (A) is opposite thymine (T), cytosine (C) is opposite guanine (G). So, the sequence CCATGA would be complementary to GGTACT. Complementary DNA strands separate on gentle heating. They bind again when cooled.
- A DNA chip is made of many different DNA sequences stuck to a flat surface. Each spot on the surface contains a different sequence.
- You can use a single strand of DNA to "probe" a solution for that strand's complement: Put in the probe, slosh it around, pull it out. If the complement is in there, it will bind onto the probe.
- A DNA microarray allows you to probe a solution for thousands of different sequences all at once. Stick each different probe at a specific spot on a flat surface. Slosh a solution containing the unknown single-stranded sequence over it. Rinse. Look for the spots where the probes found their complements.
- Microarrays can have tens of thousands of spots. This means they can look for tens of thousands of DNA sequences all at once.
- A sequencing array is made of many different short DNA sequences. Researchers use these to find the sequence of an unknown bit of DNA. A researcher chops the unknown sequence into short bits, sees where the bits bind on the array, deduces the sequences of all the short unknown bits, then reassembles the overlapping sequences into one long sequence.
- An expression array is made up of many different long DNA sequences, each complementary to every mRNA sequence that a certain cell can make. Researchers use these to study moment-to-moment changes in which genes are turned on or off. A researcher breaks a cell preparation open, extracts all the mRNA sequences it contains at that moment, and puts those on the expression array to see which ones are there. This tells the researcher which genes in the cell were turned on—being expressed, making mRNA—at the moment the cell broke open.
- Researchers love DNA chips because they give a huge amount of information, fast, at low cost.
- Doctors will soon learn to love them because there are many times when a doctor would like to know something about a patient's genes (such as whether the patient is likely to respond well to a certain drug). When the price comes down enough, microarrays will likely become routine tools in the doctor's office.