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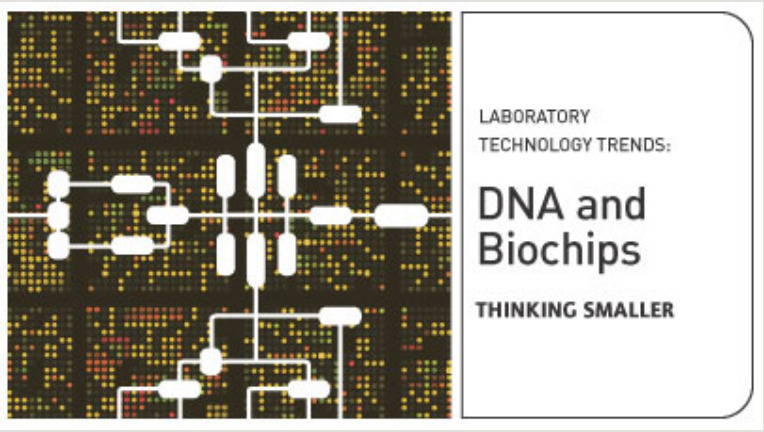

Thinking Smaller

Lab-on-a-chip techniques have recently emerged to join microarrays for routine use in life science laboratories. The two technologies frequently complement each other rather than joining in competition.

by Peter Gwynne and Gary Heebner

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This is the third of a three-part series. The first part appeared in the 4 January 2002 issue of Science *and the second in the 10 May 2002 issue.*

The world of life science research has changed dramatically over the past decade. Researchers used to working in laboratories full of glassware, stirring plates, and centrifuges now rely on miniaturized systems with tiny cards or chips that contain virtual laboratories on a microscopic scale. As the new technologies catch on, they enable researchers to do more with less — to achieve more results using smaller amounts of reagents.

Among the new technologies, DNA microarrays have already proven their value in genomics research. Pioneered by **Affymetrix** and other companies, these new research tools have proved essential in sequencing several genomes, in gene expression profiling, and in analysis of single nucleotide polymorphisms (SNPs). Much of the gene discovery from the Human Genome Project was based on the use of DNA microarrays.

Since then researchers have applied microarrays to new uses. "They are a lot more accepted," says Trevor Hawkins, senior vice president, genomics at **Amersham Biosciences**. "People are becoming very interested in looking beyond the human genome. They are very affordable for looking at other genomes. If you want a skunk genome chip, say, you can have it made for you once you have the sequence."

More recently, companies such as **Ciphergen Biosystems** have extended the principles of microarrying from DNA to more complex entities. Protein chips achieve the difficult task of directly measuring the relative levels of proteins as they react with other proteins and with different molecules. That's significant because proteins represent a key research thrust for the future. "We

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realized about three years ago that proteomics would be the next battleground for discovery, and that it's a much greater problem than DNA arrays," says Len Napolitano, deputy director of the Center for Exploratory Systems & Development at **Sandia National Laboratories**.

SOLUTIONS SEEKING PROBLEMS

Within the past year, another technology based on thinking smaller has arrived in life science research labs. Just a few years ago, microfluidics was scarcely more than a concept. Today it has become reality in the form of lab-on-a-chip products that have shown promise in a wide range of routine laboratory procedures, from sample preparation to separation. Several companies have already introduced practical laboratory research products based on microfluidics.

Like microarrays in their early years, microfluidics technologies and labs-on-a-chip must still prove their value to life scientists. "Although the technology has made an excellent start, its full potential has not yet been realized," says Tony Owen, drug discovery solutions marketing manager, Germany, for **Agilent Technologies**. "A lot of microfluidics technologies are solutions looking for problems," agrees Michael McNeely, president and CEO of microfluidics firm **BioMicro Systems**. "To date there have been very few real opportunities and products brought to commercialization that look as if they can have a positive impact."

In part, the slow development of microfluidics stems from the increasingly complex nature of the problems that it must tackle. "The general opinion is that lab-on-a-chip technology is advancing at the same pace as DNA chips some years ago," says Stefan Ståhl, chief scientific officer of Swedish firm **Affibody**. "It is advancing a lot in the protein chip area, but proteins are far more complicated in their nature than DNA in microarrays."

Dawn Madden, senior director of marketing at **ACLARA Biosciences**, summarizes the general attitude. "Microfluidics is probably less significant right now. But it will become very significant as we go forward," she says. "With microfluidics you need valuable killer applications to be put to use. It is a technology in need of a lot of applications."

In fact appropriate applications are beginning to emerge. "Over the last one and a half to two years we've been moving to routine applications for lab-on-a-chip technologies," says Mike Boyce-Jacino, vice president and chief scientific officer of **Orchid Biosciences**. "In our case processing of high throughput arrays is becoming a routine use. On the clinical side I see a lot of interest in self-contained devices for diagnostics."

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COMPETITIVE OR COMPLEMENTARY?

Not surprisingly, microfluidics finds applications in situations where the technology offers specific benefits. "You're looking to take advantage of what microfluidics does especially well," explains Darwin Asa, marketing manager for drug discovery at **Tecan**. "It's about getting better mixing, purer environments, and doing things in a sealed platform. Microfluidics platforms will be useful whenever they enable something that you can't do with a microplate."

That suggests that microfluidics technologies can complement microarrays rather than compete with them. "We see microfluidics as incredibly complementary to the suite of microarray tools we have," says Hawkins of Amersham Biosciences. "Microfluidics is extremely complementary to microarrays," agrees McNeely of BioMicro Systems. "Most of our efforts are designed to interface with existing technology systems from the perspectives of preparation and handling."

Agilent's Owen sees both competitiveness and complementarity. "To a large extent microarrays and labs-on-a-chip are different and in some ways they're similar," he says. "Array systems do one thing: They characterize in some way a mixture from a gene expression. They're not very good at quantizing. They provide answers to thousands of variations on one simple question. Microfluidics is more like chromatography. It's a more fundamental method that is very flexible and can provide answers to complex questions. It could be applied to small molecules and other samples. It has a much wider opportunity for application."

Owen's colleague Douglas Amorese, Agilent's R&D manager for microarray development, develops that theme. "I think the two systems are very complementary," he says. "Microarrays are aimed at being able to ask thousands of questions of a single sample. Labs-on-a-chip are able to process large numbers of samples and ask fewer questions of each one."

Affymetrix, the corporate father of microarrays, has sampled microfluidics. "In 1994 we received a government grant of $31 million to do lab-on-a-chip," says founder and CEO Stephen Fodor. "We demonstrated micro-PCR and microfluidics. At the time the relative value versus relative cost didn't look good. But we have the intellectual property to do it and make lab-on-a-chip technology complementary to our microarray technology."

Certainly both technologies are designed to satisfy the same ultimate needs. "Are they complementary? You bet," says Fodor. "People are demanding more and more information. And they need to know that the information they get is meaningful. The field has moved dramatically toward the delivery of knowledge. That's a pretty strong concept." Adds Owen: "The largest use for microfluidics systems today is the quality control of RNA for microarray experiments. That demonstrates the

complementarity of the two techniques."

HIGH DENSITY MICROARRAYS

A DNA chip or microarray generally consists of a slide or wafer whose surface serves as the anchor for thousands of DNA samples. The chips can have thousands of spots or features that are arranged in a regular pattern, with the location of each spot precisely known.

Production of a chip begins with a substrate such as glass or silicon. First, oligonucleotides are either synthesized in situ or spotted onto the slide using premade DNA sequences of about 25 to 30 nucleotides called n-mers; *n* stands for the number of nucleotides in each sequence. The sequences of these oligonucleotides also need to be defined so that these DNA sequences can be synthesized.

Fabricating a DNA microarray using a photolithographic technique adapted from that used by the electronics industry to make semiconductors allows for the creation of very high-density spots or features. Masks that allow light to shine onto an area of the slide direct the addition of each DNA molecule, as the oligonucleotide chains are built via a photo-activated DNA synthesis process. Because of their high cost, these masks are most suitable for producing large numbers of standard microarrays. Their advantage over spotted microarrays stems from the fact that the technique allows many arrays — 49 to 400 — to be made simultaneously rather than one at a time. In addition the technique literally builds hundreds of thousands of oligonucleotides in place on a single array. As a result, the distance between spots can be much smaller than with spotted arrays.

Affymetrix was the first company to design and fabricate ready-to-use high density DNA microarrays via photolithography. In recent years its DNA chips have increased in density and decreased in cost, making them more accessible to researchers worldwide. "You have to think about value add," says Fodor. "We will focus primarily on delivering information from the genome directly to the benchtop. To do that we will go to higher densities and higher information capacities."

GENECHIP ARRAYS AND OTHERS

One of the firm's hottest-selling products is its Human Genome U133 GeneChip array, introduced last year. "This is a two-chip set that contains over a million probes that interrogate nearly 40,000 unique transcripts across the human genome," Fodor explains. "Those comprise only about 2 percent of the known genes." The chip has a wide variety of applications from target validation to evaluating gene response to different stimulants such as drugs and environmental conditions. "There is also the clinical market, where the coverage of the known genes has become so complete that we can move toward personal medicine," Fodor says.

Two younger companies, **Febit** and **NimbleGen**, have used technology developed by **Texas Instruments** to fabricate DNA microarrays. They use micromirrors to turn light rays on and off at the location of each spot or feature, in effect taking the place of the mask that directs Affymetrix's photo-activated oligonucleotide synthesis. Computers eliminate the need for permanent masks by directing each mirror. These "virtual masks" allow quick changes to the DNA microarrays, as well as lowering the cost of making a small number of arrays.

Chief scientific officer Peer Ståhler points out the value of Febit's prototype DNA analysis instrument, called geniom one. "It is designed for biologists," he explains. "You don't need to become an expert in surface chemistry, handling, or washing steps. In addition, it is one of the first instruments in which you can use computer files on your hard disk. With a few mouse clicks you can get the process started to create the type of microarray you need — either a proven standard array selected from your hard disk or a customized array you design de novo."

The company sees individual researchers as its potential customers for geniom one. "We call it the benchtop array," Ståhler says. "One day we hope to bring back microarrays to the individual researcher rather than keep them only in central facilities."

Agilent has also eliminated the need for a physical mask in its custom oligonucleotide array fabrication. They use ink-jets as microreagent delivery devices for standard phosphoramidites and activators to precise locations where they react to synthesize 60-mer oligonucleotides. "It is a little more complicated than generating and printing a PowerPoint slide, but conceptually the same," says Amorese. "And like a PowerPoint slide it exists as a digital file that can be modified at will."

SPOTTING THE ARRAY

In a way, the field is returning to the past. Individual researchers have already made key contributions to microarray technology and production. In the mid 1990s, Patrick Brown's laboratory at **Stanford University** pioneered the technique of spotted microarrays, so called because a robotic spotter applies tiny samples of complementary DNA (cDNA) to slides. The spots are almost always larger that those created by the Affymetrix method, meaning that each array has fewer spots.

Robotic spotters use steel pins with very small surfaces to pick up DNA from a microwell plate and deposit the sample onto the surface of a slide. These systems can be programmed, allowing the researcher to develop a highly automated production system. Companies that offer robotic spotters or arrayers include **BioRobotics**, **Cartesian Technologies**, **Genetix**, and **Packard BioScience**.

Ink-jet printing is another method of depositing DNA samples onto slides or chips. Agilent has also developed a spotter that uses the ink-jetting technology originally designed for personal computer printers to deposit presynthesized DNAs. One of the advantages of this system is that there are no pins to wash after each sample is deposited on the slide; but they do, of course, require rinsing after each sample is dispensed.

Once Brown's laboratory announced its spotting technique, research laboratories around the world quickly picked it up and

started to make their own microarrays. Not surprisingly, companies saw market potential in do-it-yourself microarraying. Today, such suppliers as **BD Biosciences**, BioRobotics, **Eppendorf**, Genetix, and **Genomic Solutions** offer many of the tools that scientists can use to produce their own arrays.

Some researchers found the instruments necessary for do-it-yourself production of microarrays too expensive. But it did not take long for vendors to recognize a need for ready-to-use arrays. General purpose DNA microarrays for a number of organisms began to appear on the market. Now, Agilent, Amersham Biosciences, **Invitrogen**, **Promega**, and **Stratagene**, among other firms, offer spotted DNA microarrays for research use.

PROTEIN PROBES

While cDNA microarrays can measure the relative levels of messenger RNA expressed in a cell, they can't directly measure the proteins that those messengers produce. Protein chips on the other hand can directly measure the relative level of proteins and their interactions with other molecules. When a protein microarray is exposed to a mixture of other proteins, molecules that naturally interact with the proteins fixed on a slide will bind to those protein probes. The proteins bound to the probes can be labeled and visualized in much the same way as DNA in traditional microarrays. Molecules with strong affinities to the probes represent good candidates for leads in drug discovery, since a drug must bind to its target to be effective.

Chips to Hits

Several organizers offer scientific meetings that allow developers and users to learn about new findings in this rapidly advancing field. For example, **IBC USA Conferences** will sponsor the ninth annual Chips to Hits conference and exhibition from the 28th to the 31st of this month in the Philadelphia Marriott. The event, focusing on the application of microtechnologies to life science, will feature more than 100 scientific presentations and 115 exhibitors. New features this year include a microarray informatics forum, an advanced microarray course, and coverage of microfluidics and lab-on-a-chip technology as well as cell based assays and high content screening. You can find information about the meeting at:

www.chipstohits.com

Several companies have entered the protein chip business, among them Ciphergen, **Large Scale Biology Corporation**, **Phylos**, and **Prolinx**, **Inc**. "There's a number of players in the protein chip sector, divided into separate categories," says Roland Kozlowski, chief executive of **Sense Proteomic**, the first proteomics company to put functional array products on the market. "Some companies are working on surfaces, some on content, and some on automation and detection."

Kozlowski's firm aims to differentiate itself by providing content. "We array proteins onto our own proprietary surface, which can be integrated with any standard method of detection, including MALDI-MS," he explains. The firm's COVET technology allows the expression of many thousands of tagged proteins from any given proteome. "We're uniquely positioned to be able to handle huge numbers of proteins," Kozlowski continues. "Our main focus is on small molecule-protein interactions, enabling lead optimization, predictive toxicology, and predictive metabolism. Our technology can also be used for target ID purposes."

Prolinx has its own unique approach, via its Versalinx protein microarrays. "Most microarray technology for DNA is two-dimensional in nature," says vice president of research and development Karin Hughes. "To reduce nonspecific binding of proteins, we felt it essential to build a three-dimensional structure on the surface. That's one way in which we set ourselves apart. We also rely on our Versalinx chemical affinity tools that, among other attributes, allow us to modify proteins in solution-separate form from the immobilization step. That affords the ability to better maintain the 3-D structure and therefore the protein activity of our microarrays."

Hughes sees plenty of uses for the microarrays, which went on the market about a year ago. "In-house we've done antibody-antibody interactions, recombinant epitope reactions, peptide arrays, and even a bit of small molecule arrays," she says. "The system is quite versatile and not limited to just proteins and peptides." At present Prolinx sells the tools that customers can use to build their own arrays. "But at some point," Hughes predicts, "we will offer preprinted protein microarrays."

THE MOVE TO MICROFLUIDICS

For all their promise, protein microarrays represent just one new thrust into the application of ultrasmall technology to life science. Microfluidic devices are the latest rage in laboratory miniaturization and automation. Scientists can apply them to several routine laboratory procedures, from DNA sample preparation to chromatographic separation.

Like DNA and protein microarrays, microfluidic technologies offer several benefits. They include decreased sample volumes — meaning both the use of smaller amounts of often expensive reagents and less waste — easy automation, and potentially massive parallel processing of laboratory samples. "Microfluidics can deal with smaller quantities at faster rates than other technologies, and has the ability to integrate mechanical handling with electronic control," says Napolitano of Sandia National Laboratories.

Those abilities translate into potential financial saving. "A typical microarray's cost forces you to think about the cost of the product to be put on it," says Hawkins of Amersham Biosciences. "If a microfluidics device enables you to put on and label the sample economically, that would be a huge advantage." McNeely of BioMicro Systems makes a similar point. "The vast majority of data analysis requires much lower volumes of fluid than current preparations give you," he says. "Using microfluidics technology can save you up to 95 percent of your expense in supplies and manpower."

The channels of a microfluidic device can be as small as several microns in diameter. The movement of fluid through the tiny channels of a microfluidic device is quite different from that of a larger traditional device such as a standard flow cell or tubing. Fluid flow in microfluidic channels is laminar rather than turbulent: Mixing occurs by diffusion not active mixing. Clever design engineers can use this difference to their advantage when developing a microfluidic device.

Microfluidics is actually a technology platform rather than a single type of device. Several ways exist to move fluids through the miniature channels, ranging from electrical power to centripetal forces. The ability to harness those techniques in user-friendly ways will ultimately help determine the relative successes of the different approaches to microfluidics.

The result is inevitable. The microfluidics market is in a state of flux as individual vendors seek to establish suitable niches for their proprietary technology. In the following paragraphs we profile some of those technologies.

APPLICATIONS IN GENOMICS AND PROTEOMICS

Several companies are working on microfluidic devices for genomics, proteomics, and related research areas. ACLARA, for example, uses microfabrication and injection molding techniques to manufacture lab-on-a-chip disposable plastic products, such as its Arteas microfluidic devices, that can move solutions from one microwell to another via a microchannel about 100 microns in diameter.

The company is combining its microfluidics technology with its proprietary eTags, fluorescent labels that have unique and well defined electrophoretic mobilities. "Our eTags are used in proprietary homogeneous bioassays for genes, proteins, and cell surface antigens, which go on a microfluidics platform as well as current capillary electrophoresis [CE] systems," says Madden. The method has unique advantages of high capacity and speed, as well as efficient use of biosamples. "Experiments that were not possible are now possible using a common platform for multiple types of analytes," she continues. "In fact the platform can now be applied to the new paradigm of systems biology. We have hundreds of single fluorescence eTags, each slightly modified for different electrophoretic mobility. They separate within 20 to 30 minutes on standard CE systems — or in a minute to three minutes in a microfluidics device."

Another key benefit is the fact that the technology does not involve solid support. "It's all solution based," Madden says. "So we can look at cell surfaces and do cell based assays more effectively. Our technology takes the same fundamental approach as arrays but in solution, not the solid phase. It forms a kind of bridge between conventional assays and microfluidics technology."

Caliper Technologies, meanwhile, provides expertise in microfabrication, microfluidics, and application development. Caliper has, at times, commercialized its LabChip components through alliances with other companies; for example, Agilent uses LabChip devices in its automated 2100 bioanalyzer system for analyzing nucleic acids, proteins, and cells. The system can perform DNA sample handling, separation, detection, and data analysis in a single instrument that replaces gel electrophoresis. The system has found acceptance in checking the quality of precious RNA samples before they are analyzed on a microarray. "This application ties microfluidics and microarrays together in a useful and compelling manner," says Amorese.

The microfluidic device uses microchannels that contain a network of noncrosslinked polymers for molecular sieving. The instrument's electronics control the movement of fluids on the chip and the channel in which the separations occur. The system uses laser-induced fluorescence to detect and measure the DNA, RNA, or protein fragments in real time. "Since we introduced the instrument at the end of 1999 we've sold 1,500 instruments," says Owen. "Every month people are running more than a quarter of a million samples on the bioanalyzer. This represents one of the most successful introductions of a new analytical technology ever made." The addition of cell fluorescence assays that use pressure drive instead of electrophoresis demonstrates the technology's versatility.

Cepheid is developing fluidic cartridges for DNA analysis. This company plans to develop microfluidic systems for DNA extraction, sample preparation and processing, real-time analysis, and detection in these microscale systems. Samples of blood and other biological fluids present hefty challenges when processed in a small system. Cepheid believes its technologies measure up to those challenges.

MOVING TOWARD DRUG DISCOVERY

Several firms have started to adapt microfluidic technologies for application in drug discovery and related areas. Characterization of proteins, analysis of SNPs, and studies of potential drugs' ADME (adsorption, distribution, metabolism, and excretion) characteristics are among the targets for application.

In one commercial collaboration in the protein array field, Affibody combines unique protein binding ligands that it calls affibodies with lab-on-a-compact disc (CD) technology. The ligands offer several significant benefits over antibodies. In particular, they are easily engineered and are more stable than antibodies. "Our strength is that they are very robust proteins," says Ståhl. "We have very good experience in using affibodies in various separations."

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The collaboration intends to create CDs for use in protein characterization and drug discovery. Using combinatorial protein engineering technology applied to this CD platform, Affibody will offer an automated system to capture target proteins. "We are not developing complete chips," Ståhl explains. "Rather, we are focusing on targets and how to solve the question of detection. We are developing small, very robust affibodies of 50 or so amino acids in size. We make them very diverse and select affibodies for any particular protein."

Companies such as Orchid Biosciences have developed miniaturized systems to perform SNP analysis. Orchid's technology platform features its SNP-IT tag array, which gives customers cutting-edge genotyping capabilities. SNP-IT involves a set of biochemical reactions that isolates the precise location of a suspected SNP and then determines the identity of the SNP, using DNA polymerase that plays the key role in the method's accuracy. "We developed the tag array strategy with Affymetrix and started using it in our labs last year," says Boyce-Jacino. "We launched the full-fledged product early this year. It enables clients to move to very high volume genotyping, going from a few SNPs per sample to 2,000 per sample." The approach offers significant genotyping capacity for high volume users. It also has the major advantage of multiplexing: It can perform multiple SNP analyses simultaneously.

PFC AND ADME

BioMicro Systems focuses on drug discovery and DNA hybridization. Its core technology, passive fluid control (PFC), uses hydrophobic materials to create microscale fluidic circuits. Tiny fluidic channels that route samples in the device permit researchers to perform complex multistepprocedures by pumping samples and biochemical reagents into functional components.

"Our technology is very different from others in two fundamental ways," says McNeely. "One is simplicity; it relies on natural forces, so that you don't need complicated support equipment. Another advantage of PFC is the price point of the disposable chip. The extremely inexpensive price can be passed on to users."

The technology applies to three specific areas: immunodiagnostics, nucleic acids, and microarray processing. "Our first product, launched in May, is the first microfluidic-based microarray hybridization system for drug development," McNeely says. "The product is targeted at the individual investigator at an academic institution, government laboratory, or biotechnology or pharmaceutical company. This has a direct connection with microarray processing."

Tecan offers a LabCD microfluidics platform for high throughput ADME and toxicity assays for drug development work. The company's microfluidic systems provide all of the components needed for a high throughput ADME assay: CD-based microfluidic devices, software, and protocols and reagents. "We've tried to target those microfluidic applications not easy to do with microplates or where microfluidics has advantages," says Asa. "We've chosen to bring up the advantages of ADME because it's a big bottleneck right now."

DETECTION TECHNIQUES

The method of signal detection used with DNA chips depends on the type of label used in an experiment. Agilent, **Axon Instruments**, **Hitachi Genetic Systems**, **Molecular Devices**, and **PerkinElmer Life Sciences** offer several common tagging methods, including fluorescent, radioactive, and enzymatic methods.

Fluorescent labels are detected with confocal laser scanners specifically designed for use with DNA microarrays. Such scanners often include software to analyze and interpret the data. They can eliminate unwanted background fluorescence by limiting the distance for picking up signals to those above the plane of the array where the substrate is located. That minimizes detection of stray fluorescent signals from the substrate, dust particles, or the slide itself.

Radioactive labels can be imaged with a phosphorimager or, much less glamorous but still effective, autoradiography film. The most common radiolabels for this procedure are the phosphorus isotopes with atomic weights 32 and 33; 32P produces a stronger signal and is lower in cost while 33P produces a weaker signal that can be used over a greater range but costs more. Radiolabels are most often used with nylon membrane macroarrays such as those offered by BD Biosciences.

Enzymatic detection can also be used with nylon membrane macroarrays. But the technique is not nearly as common as the other two methods. With enzymatic systems, a spectrophotometer can be used to automate the detection process, or the membrane can be visually inspected. Both **Azign Bioscience** and **Genzyme** carry these systems for enzymatic detection.

Lynn Kielhorn, business director of **NanoDrop Technologies**, highlights a problem that has grown as researchers work with smaller and smaller volumes. "The ability to measure the concentration and quality of small samples photometrically hasn't kept pace," she says. "Researchers have had to sacrifice large amounts of valuable sample or skip the measurements." In response, NanoDrop has designed a spectrophotometer specifically for bench measurement of small samples. "The sample is deposited on a fiber optic tip and a second tip brought down to it," explains chief technology officer Charles Robertson. "The sample is drawn out like an hour glass, and we measure through the middle of that hour glass." Kielhorn points out two advantages of the technology. "It's simple to use," she says, "and it can measure concentrated samples; scientists don't have to dilute them."

Once an experiment is conducted the results need to be interpreted. DNA microarrays that contain thousands of samples or spots can produce huge volumes of data. Storing and analyzing the data can cause a serious bottleneck in laboratory research. Indeed, some researchers hope first to perform array experiments with the large comprehensive chips such as those offered by Affymetrix and then to down-size their research efforts by focusing on a specific family of genes. "You need consistency of the data," says Fodor of Affymetrix.

Today's pioneers will undoubtedly add to the body of knowledge about microfluidics and miniaturization as they develop technologies and laboratory solutions for practical applications. Given the wealth of possibilities and the number of companies entering the field, further innovation will inevitably follow.

Young Site on Aging Research

This month marks the first birthday of an online resource run by *Science*. The **SAGE Knowledge Environment** represents a pioneering effort to help the broad community of scientists interested in aging stay up-to-date on research in their field. "Specialists in aging are spread over a wide range of disciplines," says Kelly LaMarco, the site's editor. "We thought that this was a research community that would benefit from having an electronic community."

The site has four main sections: literature and news; community; resources; and highlights. Original content in the literature and news section includes commentary and review articles written by scientists as well as news articles written by journalists. Site editors rely partly on an active scientific advisory board to keep SAGE KE current in terms of coverage of new findings. Items accessed by visitors divide about evenly between articles by scientists and news articles by journalists. "We're happy we decided to include news," LaMarco says. "Our Noteworthy This Week section is quite popular with our readers." In fact scientists seem to like the entire site. About 5,000 different individuals visit the site each month, each staying there for 25 to 35 minutes on average.

As to subject matter, LaMarco says, "We focus mainly on basic mechanisms of aging and less on pure clinical papers." However, she adds, AAAS and the American Society for Family Physicians plan to introduce a website on aging for practitioners that will contain coverage of clinical studies on aging and age related diseases.

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Peter Gwynne is a freelance science writer based on Cape Cod, Massachusetts, U.S.A. Gary Heebner is a marketing consultant serving the scientific industry, based in Foristell, Missouri, U.S.A.

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