More than than gene expression

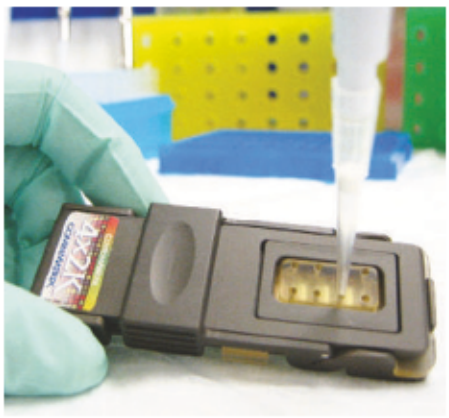
DNA microarrays are diversifying in new directions, including *in vitro* diagnostics. Diane Gershon takes a look at what's around the corner for microarray applications.

It's now ten years or so since Affymetrix of Santa Clara, California, first began selling commercial DNA microarrays. In that time, complete or partial sequences of numerous genomes, including human, have been deposited in the public databases. Coupled with recent improvements in microarray technology, this development is propelling microarrays into areas of application that extend well beyond gene-expression analysis.

It is also now generally accepted that new insights will not be gained simply by acquiring more and more gene-expression data, and that it is no longer sufficient to focus on the 25,000 or so protein-coding genes that make up roughly 2% of the human genome. Exploring the role and diversity of non-coding RNAs is equally important.

Ten years on, Affymetrix still dominates the high-density DNA microarray market. But new players have entered more recently, hoping to carve out a niche in new and emerging areas such as splice-variant or microRNA analysis (see 'It's a small world'). Others are differentiating themselves by leveraging their more flexible methods of array synthesis and offering custom-made microarrays for the human genome and a whole host of model organisms.

COMBIMATRIX



Flexibility at low density in CombiMatrix's 4 × 2K CustomArrays.

As a general rule of thumb, there are three key things to look out for when it comes to assessing DNA microarray platforms: feature density per array, flexibility (how easy it is to change the array content and design), and sensitivity. CombiMatrix of Mukilteo, Washington, an operating group of Acacia Research Corporation, concentrates on designing and manufacturing relatively low-density custom microarrays containing up-to-date content. Last month the company began offering its 4 × 2K customized microarrays for US$99, produced using its semiconductor-based *in situ* oligonucleotide synthesis method. The 4 × 2K CustomArrays contain four arrays of 2,240 oligonucleotide features per slide with a 44-μm feature size. CombiMatrix plans to offer its first high-density array early in 2006, which will have 90,000 features and a 25-μm feature size.

"We're custom, quick, flexible and cost-effective," says Michael Tognotti, vice-president of sales and marketing at CombiMatrix. There are no minimum order requirements for these arrays, which Tognotti says can be re-used up to three times, further driving down costs for researchers.

Tiling technology

But companies such as Affymetrix see less of a need for customization now that it can put whole genomes on a chip. "Affymetrix, as a result of continually shrinking the feature size, has made it practical to do experiments where

IT'S A SMALL WORLD

MicroRNAs (miRNAs) represent a new market opportunity for microarray companies (see *Nature* 435, 991–996; 2005). "MicroRNA is as hot as it could possibly be right now," says Scott Cole, head of genomics marketing at Agilent Technologies of Palo Alto, California, which expects to launch specific miRNA array-based products in 2006.

Exiqon of Vedbaek, Denmark, is now focused on developing miRNA detection products based on its locked nucleic acid (LNA) technology. "An LNA oligo will bind tighter to a DNA than a DNA itself will, and even more so to an RNA," says Mikkel Nørholm, senior research scientist at Exiqon. "Because the affinity is higher you can use a shorter probe," he says. The company offers ready-to-spot oligonucleotide capture probes based on the latest information from the miRBASE sequence database (http://microrna.sanger.ac.uk). A pre-spotted array for microRNA detection in human and mouse will be available soon.

Last month, Ambion of Austin, Texas, inked a deal with Rosetta Genomics of Rehovot, Israel, to access Rosetta's proprietary miRNA sequence database, which will add to its current range of microarrays targeting human, mouse and rat miRNAs from miRBASE. Ambion's mirVana miRNA Bioarrays are manufactured by GE Healthcare on its CodeLink platform, which uses a three-dimensional (3D) gel matrix to lift the probes off the slide surface. This is designed to maximize interaction between probe and target and enable the detection of low-abundance miRNAs.

miRNA arrays from LC Sciences of Houston, Texas, are currently available on a service basis. The addressable microfluidics chip contains almost 4,000 picolitre-volume 3D chambers and stems from work at the University of Houston and the University of Michigan. At the heart of the system is the μParaflo microfluidic technology, which enables fast *in situ* parallel synthesis of large numbers of different oligos at high yield. In addition to probes based on sequences in miRBASE, researchers can add up to 100 custom sequences at no extra charge. miRNA arrays and services are also available from GenoSensor of Tempe, Arizona, and Paradigm Array Labs of Research Triangle Park, North Carolina, a service unit of Icoria.

Scott Cole: "miRNA is as hot as it possibly could be".

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Kreatech Biotechnology of Amsterdam, The Netherlands, plans to extend its Universal Linkage System (ULS) direct labelling technology to miRNA research by offering a labelling kit optimized for small RNAs. According to Brent Keller, Kreatech's vice-president of commercial applications, ULS provides a fast and simple alternative to enzymatic labelling methods, which can be subject to 3'-end bias. "Our chemistry is independent of fragment length," says Keller, "making it ideal for miRNA applications." D.G.