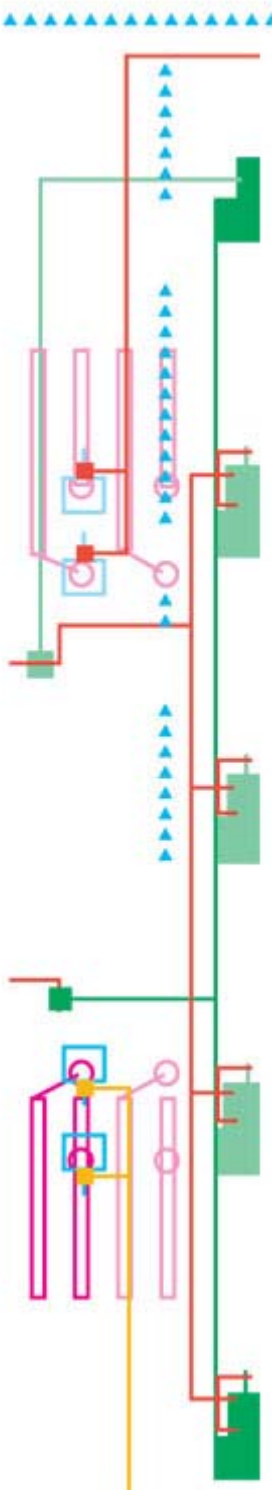
Microfluidics Meets its Market

Lab-on-a-chip companies gain momentum by a process of constant evolution

By Megan M. Stephan



It's been a busy year for the microfluidics industry. Many lab-on-a-chip manufacturers are exploring new applications such as clinical diagnostics and biodefense. Other companies are expanding and refining their current niches, moving closer to a better fit between technological capabilities and marketplace needs.[1]

According to Marlene Bourne, vice president of research and principal analyst at EmTech Research in Ann Arbor, Mich., "Two distinctive applications are driving the market: point-of-care [POC] diagnostics and life science research." POC devices perform fast analyses of blood chemistry at the hospital bedside or in a doctor's office. The market leaders in terms of unit volume are I-Stat (owned by Abbott Diagnostics, Abbott Park, Ill.) and Abaxis in Union City, Calif. Both have sold tens of millions of chips in the last year or so, at about a dollar apiece.

The revenue leaders, however, supply to life science research, generally targeting genomics or proteomics applications. These firms have shipped tens of thousands of chips, but at much higher prices, sometimes several hundred dollars apiece. Bourne pegs Caliper Life Sciences in Hopkinton, Mass., as the microfluidics leader in product sales: "Most other companies' revenues still come primarily from grants and collaborations."

Frost and Sullivan analyst Katherine Austin agrees. "Caliper is probably the biggest ... especially in high-throughput drug development," she says in an E-mail. Austin picks Cepheid, Gyros, BioTrove, Fluidigm, and Tecan, among others, as companies to watch in the life sciences sector. Overall, she predicts strong growth: "Revenues are anticipated to hit over $700 million by 2008. My feeling is that it will top $1 billion, and a $4 billion estimate is not out of the question."

DIAGNOSIS ON A CHIP

To sustain that kind of growth, companies will need to exploit new areas, and Bourne taps clinical diagnostics as the next successful market. Unlike POC devices that perform simple chemistry tests, clinical diagnostics devices would perform sophisticated biochemical analyses, using techniques such as PCR and ELISA. Initially targeted for use in clinical laboratories, these instruments could identify infectious agents or distinguish different cancers in hours, rather than the days or weeks such tests can require now. "Because this market is so vast, it will allow a lot more companies to develop a business," Bourne says. She predicts that millions of these chips could be sold at between $40 and $50 each.

Bill McMillan, vice president for biotechnology at Cepheid in Sunnyvale, Calif., says clinical diagnostics will be a "main focus" for his company over the next few years. McMillan cites breast cancer as a potential market. "Around 190,000 women are diagnosed every year," he says, and most face a "highly agonizing wait" of five days for biopsy results, suggesting a strong market for a sensitive test that reduces the wait to an hour or less.

Cepheid is designing a self-contained system that could yield results from raw samples in about two hours. A test for chronic myelogenous leukemia (CML) would start with about 200 microliters of whole blood. After cell lysis by sonication, the RNA would be captured, washed, eluted, and subjected to reverse transcriptase PCR in a series of microfluidic channels. A second PCR, detected in real time, would then measure expression of the ABL oncogene, a CML marker.

A German company, STEAG microParts, developed a credit card-sized device called the Lilliput-Chip, which could grow 96 1.8-microliter bacterial cultures at once for clinical microbiology applications. In 2004 Boehringer Ingelheim acquired the company to form Boehringer Ingelheim microParts.

Handylab of Ann Arbor, Mich., is developing a bench-top system to identify Group B *Streptococcus*, a major cause of sepsis and pneumonia in newborn infants. Handylab's instrument also uses real-time PCR, but with an electrochemical detection system rather than an optical one, potentially lowering costs.

Anup Singh and collaborators at Sandia National Laboratories in Albuquerque are developing a portable device for eventual use in dentists' offices, which will test saliva for biomarkers indicating periodontal disease. The instrument will use immunoassays to detect proteins associated with inflammation, including cytokines and tissue necrosis factors. Singh sees a "huge interest in saliva" for noninvasive sampling, and plans to explore biomarkers there for systemic diseases, such as cardiovascular disease.

DEFENSE MECHANISMS

Cepheid is also leading the way in a second rapidly growing niche, biodefense. The company has incorporated its PCR-based GeneXpert cartridge into the Biohazard Detection System developed and implemented by Northrup Grumman for the US Postal Service. Seven hundred mail-cancellation machines have already been outfitted with this technology, which samples the air for anthrax spores and provides results every one to two hours, says McMillan. The spores are vacuumed from the air, suspended in water, lysed, and then key virulence genes are detected using PCR.

MicroFluidic Systems, of Pleasanton, Calif., is also developing applications for biodefense, as well as a closely related niche, forensics. Allen Northrup, president and CEO, says the company has just delivered a PCR-based system to the FBI for automated processing of rape swabs. It also will be providing a sample-processing instrument, called the Biolyzer, to the Army and the Centers for Disease Control and Prevention. Northrup views homeland security as a strong market for some time to come. Other companies seeking a foothold in biodefense include MesoSystems Technology in Albuquerque and Microcosm in Columbia, Md.

Northrup notes that microfluidics-based biodefense applications have by necessity moved away from a strictly self-contained lab-on-a-chip format to what he calls mesofluidic systems. Pathogen detection must often be performed at a level of 10 microorganisms per milliliter or less and thus requires relatively large volumes of starting material. This constraint precludes incorporation of preliminary sample-processing steps

on a microchip. But subsequent analytical steps such as PCR take advantage of microfluidic technology to detect the small amounts of DNA generated.

Despite strong government support for biodefense, Bourne doubts this market area will take off any time soon in terms of revenue. She notes "a large chasm between where the technology is and what the market wants" with regard to response time. Mail workers and soldiers need real-time pathogen detection, but most current technologies employ delayed detection, within one-half to two hours.

Academic laboratories are already working on a fix. Susan Hua and colleagues at the University at Buffalo have developed a chip that detects toxic agents within minutes by their effects on the volumes of cells residing on the chip. Cells act as natural resistors, preventing the passage of electrical current when they swell, and allowing it when they shrink. The chip can measure such changes almost instantaneously. This chip could also be used for clinical applications, such as rapidly measuring bacterial sensitivity to antibiotics.

THE BREAD AND BUTTER

Exciting as these applications are, the industry's "bread and butter" is still life-science research, says Bourne. Companies such as Caliper thrive by providing microfluidic-based replacements for standard laboratory methods such as gel electrophoresis and high-performance liquid chromatography (HPLC). Because they are faster and use smaller sample amounts, microfluidic methods are more compatible with the large-scale genomics and proteomics efforts now underway at many drug companies.

Michele Boudreau, Caliper spokesperson, says the company recently sold its one-millionth chip for the 2100 Bioanalyzer, a gel-electrophoresis instrument produced with Agilent Technologies of Palo Alto, Calif. Caliper has also introduced second-generation chips for Agilent's new automated 5100 Bioanalyzer; for new partner Bio-Rad Laboratories' Experion system; and for a newer, more robust and cost-effective system of its own, the LabChip 3000, which is now in use at several large drug companies, including Merck and Johnson & Johnson.

Agilent has recently introduced the HPLC-chip, which integrates sample enrichment, HPLC, and electrospray emission on a single chip for mass spectrometry-based proteomics. This device nearly epitomizes the lab-on-a-chip promise: small sample size, ease of use, speed, and reliability, in service of a technically demanding application. But Agilent has competition in the HPLC market, including Eksigent Technologies in Livermore, Calif., and Nanostream in Pasadena, Calif. Nanostream recently released a second-generation Brio cartridge for its Veloce microparallel liquid chromatography system that can handle larger sample sizes.

Aviva Biosciences of San Diego and others are delving into electrophysiology, useful for testing ion-channel activity in cardiac cells and neurons, for instance (see related story, page 18). Aviva vice president of research and development, Jia Xu, says the company is finding a "very big market" for its SealChip, which Molecular Devices sells as part of the PatchXpress system. With more than 50 instruments now deployed, PatchXpress is "becoming the standard for cardiac safety," he says.

Fluidigm of South San Francisco has focused on structural biology, by developing chips and hardware to simplify the protein crystallization process. Kevin Farrell, TOPAZ product line manager, says the chips have caught on well, resulting in more than 25 solved structures including integrin $\alpha_{IIb}\beta_3$, solved by Timothy

Springer's group at Harvard University.[2] The company's next-generation TOPAZ chips will screen as many as 768 crystallization conditions simultaneously.

Fluidigm is now looking to apply its high-density technology to DNA as well. The Digital Isolation and Detection Chip can partition a DNA mixture into as many as 10,000 5-nanoliter wells for PCR. This procedure allows detection of rare mutant alleles (for instance, those present in a few malignant cells) by effectively enriching for the mutant DNA. "This technology could be really enabling," says marketing director Chris Heid, since this number of samples would not be practical using individual tubes or even microplates.

Like Fluidigm, BioTrove of Woburn, Mass., is also refining its technology based on the experiences of early adopters, says chief technology officer Colin Brenan. The company recently introduced a nanofluidics-based, high-throughput screening device, the OpenArray Transcription Analysis System, which can screen drugs for their effects on many genes at once.

In general, Brenan says, though still "an emergent field," microfluidics seems to have overcome its initial difficulties. "Lots of companies have started to take advantage of the momentum," he says, predicting another busy and successful year ahead.

References

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