Game-changing microfluidics

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The Quake laboratory's MITOMI chip, designed for the rapid screening of molecular interactions, is providing a foundation for ongoing research at MSB. Credit: Bill Burkholder, MSB, IMRE, A*STAR

The development of miniaturization strategies that integrate several laboratory functions on a single chip is benefiting many areas of biomedical research, making even complex experiments faster and cheaper to perform. These 'lab on a chip' systems, generally known as microfluidic devices, are typically composed of small polymer wafers patterned with precisely engineered microscopic channels, reservoirs and valves that can transport tiny volumes of fluid with remarkable precision.

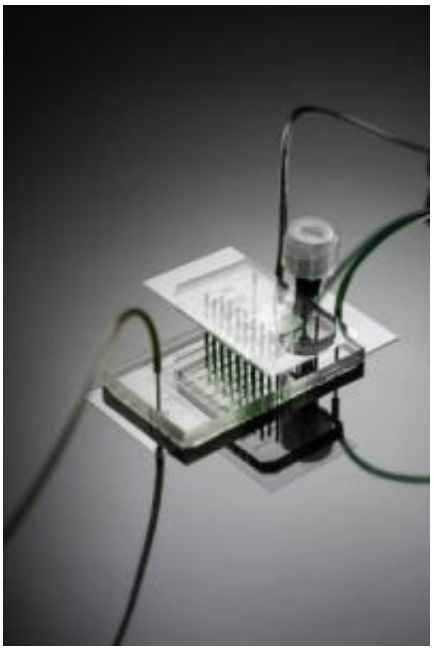
"Microfluidics offers key advantages for bioanalytical and diagnostic applications, including faster analysis and response times, better process control and high throughput on a cost-effective, disposable chip,"

explains Zhiping Wang, manager of the Microfluidics Manufacturing Programme at the Singapore Institute of Manufacturing Technology (SIMTech).

Putting principles into practice

SIMTech is just one of several A*STAR centers exploring microfluidics, and A*STAR recently demonstrated its commitment to this technology with the launch of the Microfluidics Systems Biology (MSB) laboratory at the Institute of Materials Research and Engineering (IMRE). To head up the project, they turned to Stephen Quake, a Stanford University researcher who has focused on developing cutting-edge microfluidic devices for biological applications.

Quake already had strong ties to the Singapore research community through his company Fluidigm, which bases its manufacturing operations in the country, but he also recognized the MSB as a new opportunity for interdisciplinary collaboration. “The initial idea was to start applying some of the technologies we developed at Stanford, and using them to advance the frontiers of science,” he says. “I wanted to make contact with people working on biology and genomics and materials science.”



The 3D HepaTox chip, devised by Hanry Yu's team at the IBN, enables researchers to assess the physiological effects of eight different compounds on cultured liver cells simultaneously. Credit: IBN, A*STAR

Quake collaborated with Stanford colleague William Burkholder, a microbiologist who is co-principal investigator at the MSB alongside IMRE scientist Yin Thai Chan, and the three have been working on a variety of projects since August 2010. One of the primary objectives of the MSB is to transform experimental microfluidic devices into a working engine for scientific discovery. "Our key performance indicators are going to be publications, because we really want to keep the focus of the group on doing high-impact biology," says Burkholder.

The majority of MSB projects emphasize the use of microfluidic tools to generate large quantities of high-quality biological data, such as mapping the way that proteins interact with each other or with chromosomal DNA, or generating high-quality genomic sequence data from single cells. One current project focuses on optimizing the 'MITOMI' chip, a

device developed in the Quake lab that offers a high-throughput platform for measuring the binding affinity of proteins known as transcription factors for target DNA sequences. “We invented the device to observe how biological molecules stick to each other and how strongly they do so, and to run experiments in parallel using tiny amounts of sample,” says Quake. Current versions of the device can screen up to 4,000 sets of interactions at a time, and he and Burkholder are now using such devices to characterize the function of key gene regulators within human cells.

Chips for every occasion

A growing number of laboratories in Singapore are investigating the far-reaching applications of microfluidics. Some of the most advanced applications of the technology currently involve analyzing environmental or biological samples in order to detect infectious agents or toxic contaminants. A*STAR scientists have already made considerable progress in this field.

A research group at the Institute of Biotechnology and Nanotechnology (IBN) has designed an all-in-one chip that can be used in the diagnosis of influenza from a patient nasal swab sample within a couple of hours. This MicroKit technology, which was selected as a finalist for the Wall Street Journal’s Asian Innovation Awards in 2011, has already been licensed for commercial development, and the IBN is now engaged in trials to test its efficacy at detecting pathogenic bacteria in clinical settings.

Meanwhile, Abdur Rub Abdur Rahman and colleagues at the Institute of Microelectronics (IME) are using microfluidics to hunt another kind of threat—the circulating tumor cells (CTCs) that lay the groundwork for metastatic invasion in cancer. “CTC detection is a proverbial ‘needle in the haystack’ problem,” explains Rahman. “CTCs are extremely rare in

blood—there may be one CTC per milliliter as opposed to one billion red blood cells per milliliter—and harvesting these cells reliably and reproducibly is a challenge."

The system being developed at the IME uses magnetic beads to capture and enable the detection of these extremely scarce CTCs with relative ease. The present prototype platform delivers results in less than half a day. Rahman also points out that this approach eliminates many of the 'moving parts' that can confound conventional analysis. "We want to avoid all manual processing steps, including optical microscopy for cell recognition and enumeration, which is a mainstay in many contemporary systems," he says.

A research team led by Hanry Yu at the IBN is investigating how to manipulate the flow of liquid and nutrients within a microfluidic cell culture system to create conditions that mimic the natural environment of tissues within the human body. The IBN team seeded liver cells within a microfluidic system, creating a 'microtissue' that can be used to characterize the liver's capacity to metabolize and process different drugs and other compounds. "This method saves precious human liver cells, as it requires only a few thousand cells per assay," says Yu. "It is easy to change the media to test complex drug treatment schemes in order to design optimal treatment strategies." The method might also be useful early on in the drug discovery process by reducing the amount of a drug candidate that is required for screening. The current generation of the IBN's three-dimensional HepaTox chip features eight channels, enabling investigators to screen multiple compounds in parallel.

Although the liver is a major destination for drugs, Yu envisions similar three-dimensional culture systems being used to model other organs, such as the kidney and pancreas. Yu and his colleagues have already begun experimenting with a 'human-on-a-chip' prototype, which enables cultivation of four different cell types, each of which resides within its

own channel but can simultaneously be exposed to the same fluid environment.

Small chips ready for the big time

While commercialization is often the best way for research seeds to achieve maximum impact, transitioning from a functional prototype to a mass-produced device presents numerous logistical challenges. “The biggest challenge in the area of microfluidics device manufacturing is reducing the production cost from several dollars per device to a few tens of cents per device,” says Wang. His team at SIMTech is focusing heavily on large-scale manufacturing, and has already developed a chip for monitoring water quality and a ‘micromixer’ device that can efficiently combine polymers, which is currently being tested by a major pharmaceutical company.

In September, SIMTech launches a new Microfluidics Foundry operation, a dedicated center for microfluidic device research, development and manufacturing. “The Foundry will provide design, prototyping and production services to laboratories in universities and research institutions as well as companies worldwide,” says Wang.

Optimization for consumer use is another key objective of the MSB. “The most basic goal of the lab is to give fresh life to devices that have been prototyped but are not widely available to the biological community,” says Burkholder. “We aim to transform devices that can work with expert assistance on a benchtop into user-friendly products that can be purchased from a catalogue.” MSB scientists have begun investigating the potential of adapting their MITOMI chip for use in drug discovery applications.

With the growing number of laboratories across Singapore now exploring microfluidic tool development, an increasing amount of

collaborative research is expected to advance the field further. “We organized the first community-wide microfluidics conference in Singapore earlier this year,” says Quake. “I was very impressed with the breadth of the research that’s going on—there is really a wonderful community that has sprung up.”

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