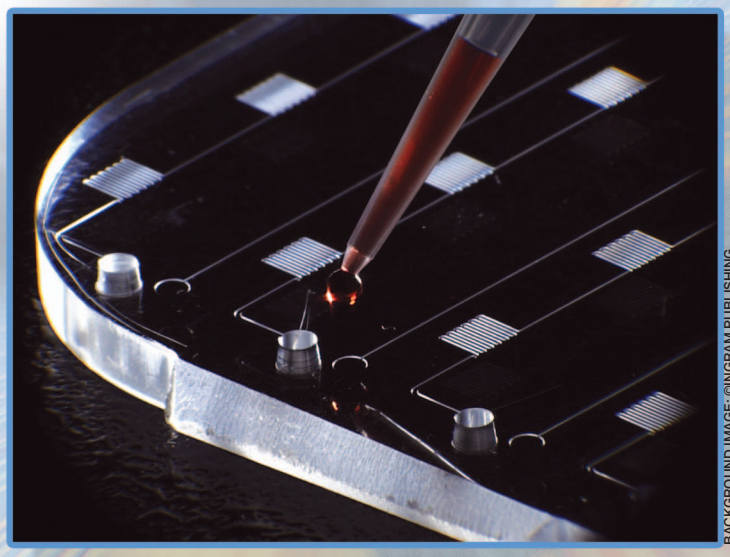
The Right Tool for the Job

By Leslie Mertz



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From Microchips to Artificial Tissues, Experts Say BioMEMS Are Poised to Invade Medicine

In the biological world, where the typical human cell is less than 10 µm in diameter, an average bacterium a few micrometers long, and the garden-variety virus about 100 nm in length, more and more researchers view microscopic tools known as biological microelectromechanical systems (bioMEMS) as the right choice for keeping patients alive and healthy. BioMEMS are an outgrowth of MEMS—the sensors, actuators, and other microchips—developed for the electronics industry. MEMS are present in everything from computers and ink-jet printers to automobile air bags and digital video projection systems.

BioMEMS are MEMS directed mainly toward biomedical uses. Today, for instance, a person goes to a medical laboratory to have blood drawn, and in a week or two, gets the results from the doctor. The costs for such tests can run into hundreds. On the other hand, with new bioMEMS technology that is on the horizon, the same person could prick a finger, deposit a drop of blood on a small testing cartridge, and read the results in a few minutes—all without ever leaving home. Not only would this eliminate a trip to the laboratory, but it would also greatly decrease the amount of blood needed for testing. In addition, it would reduce the amount of reagents required to perform the blood test, and this would help to lower costs.

"The idea is to build systems that can be used to detect cells, or to detect bacteria or viruses or proteins," said Rashid Bashir, Ph.D., Abel Bliss professor in the departments of electrical and computer engineering and bioengineering, and director of the Micro and Nanotechnology Laboratory at the University of Illinois at Urbana-Champaign. "Today, we make chips that go into every watch, every calculator, every iPad, every phone. The more we make, the lower the cost. We want bioMEMS technology to be just as pervasive."

BioMEMS are already doing or have the potential to do many medical tasks faster, better, and cheaper than traditional methods. A few examples are

- quick scanning for and diagnosis of a profusion of diseases from a single drop of blood
- generation of artificial tissues that can help a patient's damaged organ to function again

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- testing of drugs without animal experimentation
- identification of the earliest signs that cancer is spreading, allowing doctors to provide more effective treatment
- highly accurate, yet inexpensive, easy-to-use, and easy-to-interpret patient diagnostics in Third World nations, where hospitals are few and far between.

"We are at the beginning of this technology being applied to applications," said Bashir. "There has been a lot of R&D done, and there is still a lot of R&D to be done specifically when it comes to understanding the basic mechanisms of disease, but in terms of medical applications, many of them are now on the horizon, and new start-ups and other companies are beginning to adopt these technologies." Up-and-coming bioMEMS companies are diverse, but many focus on lab-on-a-chip technologies that are being designed to perform blood tests more quickly and less expensively than those offered by traditional diagnostic laboratories. He added, "We face many manufacturing and technical challenges, and we may face financial and other challenges, but the possibilities are tremendous, and it is a very exciting time to be working in this field. I believe a lot will happen in the next 10 years or so."

Diagnostics and Therapeutics

One of the hottest areas for bioMEMS is diagnostics: taking a small sample of blood or other bodily fluid from a patient and testing it for various diseases right at the bedside, rather than sending it out to a laboratory and waiting a day or more for the results.

"It turns out that today, the most prescribed tests in medicine are the blood tests," said Mehmet Toner, Ph.D., Helen Andrus Benedict Professor of biomedical engineering at Massachusetts General Hospital, Harvard Medical School, and director of the BioMEMS Resource Center. "We typically measure complete blood counts, electrolytes, glucose, several biomarkers, and other things. However, these measurements are rather nonspecific." If the blood work reports something abnormal, perhaps too-low or too-high readings of certain white blood cells, he said, a doctor typically orders additional examinations, some of which may be expensive imaging tests, such as X-rays or a magnetic resonance imaging scan.

With bioMEMS, the blood test would be enough to provide a detailed medical diagnosis. "The blood has pretty much every bit of information you need regarding your health. You can almost diagnose and monitor every single disease—from Alzheimer's to cancer to prenatal conditions to infectious diseases—from the blood," Toner asserted. "What these microtechnologies are enabling is the ability to access the cells and proteins and other disease markers that are in blood, that simply were not possible to read in the past."

An improved understanding of microfluidics, or how extremely small volumes of fluid behave, is vital to those advancements. This is because bioMEMS usually require that blood or other bodily fluids move through miniscule channels built onto a tiny electronic chip so that sensors can read the fluid's components. However, the physics of fluid movement is different at the microscale than it is at larger scales. As Toner noted, "The ability to precisely control the flow and conditions is very important, especially when you are looking for low-abundant proteins and various rare cells within the blood. BioMEMS technology gives us the ability to access even rare particles, cells, and molecular species in the blood, and that opens up whole new possibilities."

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Counting Blood Cells and Bacteria

"In our group, there's a big thrust on diagnostics and biosensing, and the use of microfluidics and microelectronics in biochips," said Bashir, noting that his laboratory is interested in developing point-of-care sensors, which can analyze the sample and provide results right at the bedside. The model is the finger-prick test that people with diabetes use to check their blood-glucose levels. "That's kind of the Holy Grail in terms of taking just a drop of blood and getting some useful diagnostic information from it, but that's really the only example that you see today on the market. Why can't we have more examples like that for other important applications? Our goal is to build devices of that type with silicon or different materials." His laboratory is developing a biochip that can provide a full blood-cell count (Figure 1).

In a nonhuman project, Bashir is also working with the U.S. Department of Agriculture to create biochips that can quickly check food for bacterial pathogens, such as *Escherichia coli*, *Listeria*, and *Salmonella*. "The goal is to rapidly detect the presence of live bacteria from fluid samples," he said. Together with Laila Razouk, Ph.D., an engineer specializing in microdevices, he helped to create a company to continue developing the biochip. The company called *BioVitesse, Inc.*, is located in the San Francisco Bay area.

Finding Rare Tumor Cells

One bioMEMS project that has received considerable press is a large project on cancer diagnosis led by Toner and Daniel Haber, M.D., Ph.D., director of the Massachusetts General Hospital Cancer Center and the Kurt J. Isselbacher/Peter D. Schwartz

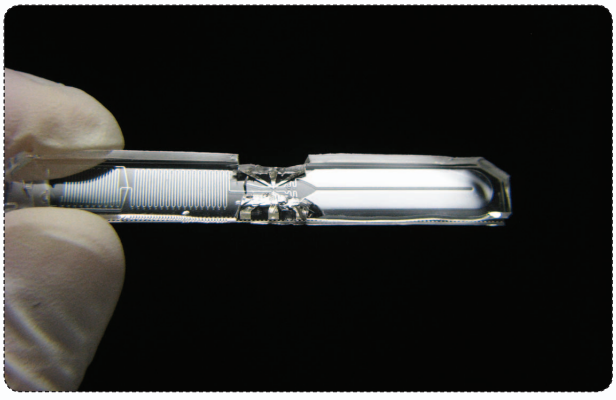

FIGURE 1 Rashid Bashir's research group developed this device, which counts white blood cells from a whole-blood sample. It is made with polydimethylsiloxane (silicone), glass, and metal electrodes. (Photo courtesy of Rashid Bashir.)

Professor of Oncology at Harvard Medical School. In this project, sensors find the elusive cancer cells that spread the disease from one part of the body to another. "Cancer doesn't kill because of the primary tumor. Nine out of 10 times, it kills because it spreads," Toner said. "We've never been able to find these cells in transit through the peripheral blood because they are so rare: They are maybe one in a billion blood cells."

Toner is working with the National Institutes of Health, health-care giant Johnson & Johnson, the charitable program Stand Up to Cancer, and a number of other organizations to develop biochips that will find the rare, circulating tumor cells in the blood. "We needed technologies that are extremely sensitive to find one cell in a billion blood cells. The question was, 'Can we develop the right technology to find them?' We can. We developed a microchip that can do that," he said.

The announcement about the development of the chip in 2007 generated great interest throughout engineering and biomedical circles, and energized the idea that bioMEMS has a wealth of applications for cancer diagnosis and therapy. "You could monitor the tumor load in circulation and know if your treatment is effective; you could look for early relapse and treat them immediately; you could use it for early detection. The applications are so broad that people believe that if this technology pans out, it has the potential to turn cancer into a chronic disease, like AIDS or diabetes."

Toner's chip is undergoing clinical trials at Massachusetts General Hospital, the Dana-Farber Cancer Institute in Boston, Memorial Sloan-Kettering Cancer Center in New York and New Jersey, and the M. D. Anderson Cancer Centers in Texas. Marketing will follow, but in the meantime, he is continuing to refine the chip. "It will afford the ability to monitor cancer patients individually, so it is personalized medicine at its best. It gets genetic as well as cellular information about the progression of their cancer, how the drugs are working on their cancer, and does that non-invasively with a simple test. It's very powerful."

Additional Cancer Work

Other bioMEMS cancer projects are underway elsewhere. Bashir, for instance, is working on a project for the National Institutes of Health to build a silicon biochip that can detect cancer markers in the blood. "The idea is to take, for example, a very small biopsy sample from a breast-cancer patient, and be able to look for the specific expression of certain proteins to indicate whether that patient's therapy is working or not." That project is still in the research and development phase.

FIGURE 2 The low-cost mChip could be especially beneficial in the developing world such as this African settlement where the HIV and syphilis infection rates are high. (Photo courtesy of Samuel Sia.)

In Woburn, Massachusetts, researchers at Claros Diagnostics hope to soon market a quick and easy prostate-specific antigen (PSA) test, said Samuel Sia, a professor of biomedical engineering at Columbia University. He is one of the company's three cofounders and also the chair of its scientific advisory board. The device, which was approved in Europe last year, runs the PSA test and provides results in about 15 min. This is compared with the one to two days required for the currently used tests, which must go out to a laboratory for analysis.

Doctors routinely monitor PSA levels in men who have prostate cancer to track the disease's progression and also to follow up with those who have undergone prostate surgery to make sure the cancer hasn't returned. A faster result would benefit the health-care provider as well as anxious patients, Sia said. "The ability to perform diagnostics where the patients are would enable healthcare to be delivered more efficiently."

Claros's test consists of a hard-plastic cassette, which is lined with channels that hold the series of reagents needed for the analysis. Using vacuum, the cassette draws in the blood sample, the reagents and blood interact, and a reader provides the outcome.

Proprietary injection molding technologies allow the company to produce the intricate cassettes quickly and at a reasonable price: one cassette takes about 15 s to produce and costs around a dime, Sia said. "Injection molding is a technique commonly used to produce consumer products at a massive scale and for low cost. Traditionally, it was difficult to do with very small features," he said, but the company was able to accomplish it. "Claros has developed a suite of techniques to make the production of these cassettes rival the cost of cheap lateral-flow tests."

Fighting Disease in Developing Countries

One of the Bashir group's efforts is to fight human immunodeficiency virus (HIV) where it is most insidious: in the Third World nations of Africa (Figure 2). Specifically, he is developing a microchip that can count certain types of white blood cells, called *CD4-positive cells*, which are associated with HIV infection. HIV damages these cells, which results in a lower count of functioning CD4-positive cells. With such information in hand, doctors can track the progression of the infection and disease, and prescribe appropriate treatment for individual patients.

That research has advanced enough that Bill Rodriguez, M.D., former chief medical officer of the William J. Clinton Foundation, and Toner have started a company called *Daktari Diagnostics* in Cambridge, Massachusetts, to continue developing the CD4 device. Toner and Bashir, who are coinventors of the CD4 microchip that underlies Daktari's CD4 counting technology, also sit on the company's advisory board, along with a third coinventor, Xuanhong Cheng, Ph.D., the P. C. Rossin assistant professor of bioengineering and materials science and engineering at Lehigh University. "The company has made a lot of progress in getting to a point where we can make robust sensors,

and now in the next few years, we plan to do more testing with patient samples," Bashir said.

Sia and his colleagues have developed a microchip, called the *mChip*, to detect both HIV and syphilis (Figure 3). The device exposes a drop of blood to a series of reagents and produces easy-to-read results in a matter of minutes (Figure 4). The research group tested the chip in Rwanda, where the rates of HIV infection and syphilis are very high, and found that it could correctly identify the two conditions almost 99% of the time.

Despite the success, the mChip is not available commercially yet, Sia said. "A main hurdle is that funding is not often easily available for neglected diseases," he explained. Nonetheless, the research team is continuing to develop the chip. "We have active ongoing projects to expand the panel of infectious diseases that the mChip can detect in resource-limited settings," he said, listing potential disease candidates as hepatitis B and C, herpes, gonorrhea, and chlamydia.

Sia emphasized the importance of this work. "Take syphilis as an example. It causes stillbirths and congenital defects, but can be easily cured with penicillin if the patient is diagnosed in time. In developing countries, hundreds of thousands of people are dying every year due to the lack of a point-of-care syphilis test. The numbers are astounding," he said. The mChip, complete with the biochip, chemicals, and packaging, would run an estimated US$ 2.00–3.00 each, making it an economically viable diagnostic tool. "A low-cost test in these settings can dramatically ease human suffering."

Bashir noted that the use of bioMEMS can also easily expand to other needed medical diagnostic applications in resource-limited developing countries. "Can we have chip-based sensors where you'd need just a drop of blood to detect TB or malaria, or to sense other specific pathogens or cells?" With this biochip technology, any person anywhere could test his or her blood with a chip-containing cartridge, connect that cartridge to a cell phone or some other sort of wireless device, send the data for a quick analysis, and properly dispose of the used cartridge. "The notion of microchips used for diagnostics could be as pervasive as the use of microchips in iPads or phones," he remarked.

"One of the grand challenges that faces the U.S., the world and our society in general is health care. How do you manage healthcare? How do you deliver healthcare that is affordable to all and that is available to all? That is a basic right," Bashir noted. "We hope to use this technology to help us address some of these important issues."

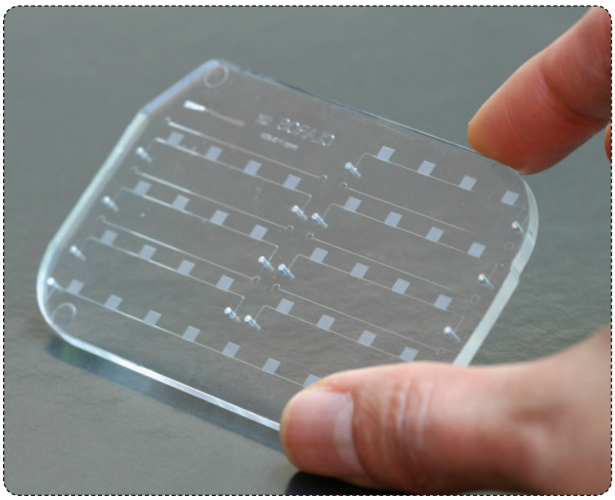

FIGURE 3 Sia and his colleagues have developed the mChip, which detects both HIV and syphilis. (Photo courtesy of Samuel Sia.)

Tissue Engineering for Transplantation

Tissue engineering using bioMEMS is just beginning, but it is already a vibrant research area. Some laboratories continue to perform some conventional tissue engineering without bioMEMS technology, especially those laboratories making skin and cartilage, which are already clinically available. This is possible because skin and cartilage require few blood vessels to function, while complex tissues, which occur in major organs such as the heart or liver, demand a network of capillaries, said Ali Khademhosseini, Ph.D., associate professor at Harvard Medical School. "This is where bioMEMS starts playing a role."

He explained that tissue engineering may be an answer to a particularly vexing health problem: the lack of available organs for transplantation. "There is a long waiting list, and someone has to die for a patient to be able to get an organ in most cases. How do we address that? Generating artificial tissues is one way to do it." In response, his laboratory is recreating artificial tissue that works like normal human tissue. "We can't just use cells alone, because tissues actually have a lot of architecture associated with them, and this architecture affects the function," he said. "By using these microfabricated technologies, we can actually start to recreate some of these architectures so that our engineered tissues not only resemble natural tissues, but also function more like natural tissues."

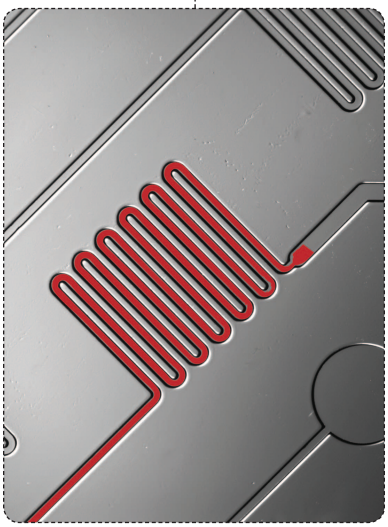

FIGURE 4 When added to the mChip, a drop of blood moves through miniscule channels where it is exposed to a series of reagents. This produces easy-to-read results in few minutes. (Photo courtesy of Samuel Sia.)

One of the architectural elements is the collection of capillaries, the tiniest of blood vessels that permeate tissues and keep them alive. Using adult or embryonic cells and stem cells, along with various biomaterials, his laboratory employs bioMEMS technology to construct miniscule fluidic channels into the shape of a capillary network and add them to the engineered tissue. "We are creating the vascularization," he said. "We are applying the same technologies that the microelectronics industry uses to make cell phone and computer chips, but using degradable materials that cells will interact with. In other words, we are generating the kinds of tissue structures

that cells can integrate into and therefore have a much more functional behavior."

In addition, the microfabricated environments that his laboratory creates also help to control the body's cells, pushing them to take on the duties of specific types of organ tissue. "By doing this, we can then kind of signal the cell about what it should do and direct its behavior in a much more predictable way." The resulting engineered material can take the place of damaged, lost, or diseased tissue. "If we can transplant tissues that are compatible with the body, then we can restore a lot of a patient's lost functions. In diabetes, for example, the pancreas often does not work properly, so if we can restore that function, it would be great."

Drug Testing

Besides using artificial tissues for transplantation purposes, they show promise for drug testing. Currently, scientists develop a drug candidate, spend many, many weeks testing it on animals, and if all goes well, proceed to human testing, which can take many, many months. Negative findings along the way can send the scientists back to the drawing board. However, with artificial tissues, scientists can test a large number of drug candidates simultaneously and without the costly and sometimes inconclusive animal testing.

Khademhosseini's research group hopes to put the engineered tissues and cells on biochips for use in drug testing. "If we can make engineered human tissues that behave and function like natural human tissues, then we can do a lot of the testing of chemicals and drugs more efficiently and effectively. That will allow us, first of all, to eliminate animal testing." Not only is animal testing a long and expensive undertaking, he said, but the results often aren't translatable to humans. "A mouse does not behave in the same way to a particular chemical as a human does. So if we can actually make human tissues, then we can eliminate these differences between how an experimental animal responds to drugs and how a human responds."

As an example, researchers could construct engineered tissue to mimic human cancerous tissue. "That gives us a model of cancer. Then we can test different drugs against this cancer model in a dish and see which drugs work the best," he noted. Unlike animal testing, which is performed one drug at a time, the work with engineered tissue can proceed much more efficiently. He added, "We can not only do orders of magnitude more testing than what's currently done, but we can also do it a lot cheaper."

Drug testing with engineered tissues is a new field, but it will become more prevalent, he predicted. "For really widespread application, I think it's still going to take a few more years, but definitely I think the opportunity is there. It's become a very dynamic field that many researchers are working on and trying to push forward."

Drug delivery may also benefit from bioMEMS, Khademhosseini said. He proposed using bioMEMS technologies to generate differently shaped micro- and nanoparticles, and then encapsulating drugs within the particles. "If you inject the same drug into the circulation, but encapsulate the drug in differently shaped nanoparticles, these particles would go to different parts of the body," he said. This would allow for targeted drug delivery, which could decrease the amount of drugs patients need and also cut back on any potential side effects.

Past, Present, and Future

"If you look historically at how bioMEMS evolved, the process involved mostly understanding fluidic flow and biological sensing at the micro- and nanoscales. We didn't know the physics of fluids at that length scale very well," Toner said.

Although some questions still remain, researchers gained enough knowledge over the years to begin making actual devices. "Some of the early MEMS devices go back to the late 1970s," he said. Since then, the emphasis has been on making things tinier and tinier. "Investigators were so driven with the idea of building smaller things that it was almost like going to the Wild West and putting a flag on the ground saying, 'This is my ground.' Investigators were making the next smallest electrophoresis device or flow cytometer or chromatography device. There was a lot of miniaturization for miniaturization's sake and impressive engineering achievements, while the search for truly enabling applications was falling behind technology development." At the same time, he said, researchers were gaining insight into and experience with the manufacture of MEMS and bioMEMS, and learning about both the sensitivities and limitations of the devices.

This expanding foundation of understanding has made possible medical applications that will change the way medicine is done. As the field of bioMEMS matures, many laboratory tests will occur at home with a simple prick of the finger and have results delivered in minutes rather than days; faster test results will help doctors modify treatments for individual patients; new drugs will find their way to the bedside faster as multiple drug candidates go through screening simultaneously and without the need for animal testing; the shortage of donated organs will begin to diminish; and point-of-care devices will allow people in developing countries to receive far-improved care.

Other current or forthcoming bioMEMS applications include electrode arrays that act as artificial retinas for use in patients with macular degeneration and retinitis pigmentosa; new and improved instruments for image-guided surgery; easy-to-swallow imaging devices (endoscopes) that reveal internal organs and body cavities without patient discomfort; DNA microarrays to study gene activity and to detect genes and mutations; and sensors for environmental testing, including the rapid detection of pathogens. The possibilities are seemingly endless.

"What's happened over the last five years or so is that all of this knowledge is coming together in a very positive way: People have started exploring exciting clinical and biological applications for these devices, because we now understand it enough to manufacture them in the research lab and in the factory," Toner said.

He added, "It's taken 30 years, but the field, in my view, is at an inflection point where we are finally exploring some value-added applications. It's becoming quite exciting."

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