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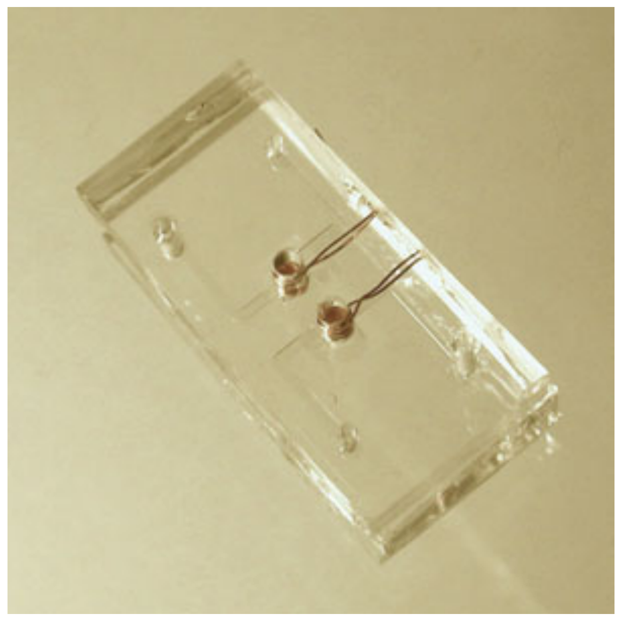
Diagnostic Magnetic Resonance – Miniature System Could Have Huge Public Health Impact: January 29, 2010



The microfluidic device for TB detection integrates membrane filters and microcoils to concentrate and detect bacteria via NMR. Bacteria were targeted with highly magnetic nanoparticles for sensing. Credit: Hakho Lee

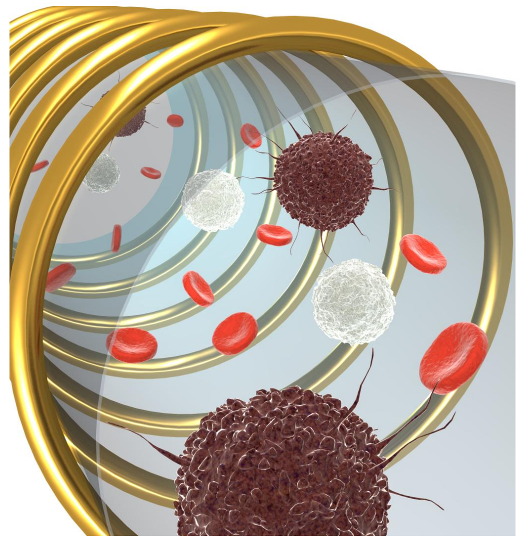
According to the World Health Organization, one-third of the world's population is infected with tuberculosis (TB), with the majority of deaths occurring in the developing world. Imagine you were part of a resource-deprived mobile clinic in South Africa. To screen for TB infection, you most likely would use a 19th century technique called sputum smear microscopy. Although the technique is cheap and fast, it is not very sensitive, and you probably would miss many cases. A more sensitive approach is to wait 1–3 weeks to grow TB bacteria from the sputum sample; that is, if you have a laboratory, trained staff, and precious time to spare. Each person with active TB who goes undiagnosed will infect 10 to 15 people per year. To combat spread of the disease and offer timely treatment, an inexpensive and sensitive diagnostic method is needed that could be applied in the field without the need for sample preparation. A Harvard University research team may already have a solution in their hands.

In the past decade, scientists have explored using magnetic nanoparticles as chemical sensors for detection of DNA sequences, proteins, antibodies, hormones, metabolites, and cells. In contrast to optical techniques, magnetic resonance-based detection allows for sensitive measurements in opaque biological samples, such as blood, urine, and sputum. However, conventional magnetic resonance sensors or even desktop nuclear magnetic resonance (NMR) machines are not suitable as point-of-care (POC) instruments because they can measure only one sample at a time, require relatively large amounts of sample, and can weigh more than 90 pounds. Harvard University Medical School researchers Ralph Weissleder, Professor of Radiology and Systems Biology and Director of the Center for Systems Biology, and Hakho Lee, Instructor in Biomedical Engineering, realized that the required amount of sample could be reduced substantially by scaling down the entire device. Using standard microfabrication techniques, they constructed a chip-based NMR device that measures 2 x 7 inches, about the size of a cell phone. “To our knowledge, as of now, this is the smallest NMR system ever built and costs less than $200,” says Lee.

The microNMR chip contains microcoils (used for radiofrequency excitation and NMR signal detection), a small portable magnet, a microfluidic network for sample handling, and NMR electronics. The $1 microfluidic part is disposable, whereas the rest of the device can be re-used. Magnetic nanoparticles used in the device are composed of an iron oxide core surrounded by a polymer. The nanoparticles can be custom-coated with small molecules or antibodies that act like chemical glue to specifically bind target molecules in a biological sample. Upon binding to their molecular target, the nanoparticles form clusters, which leads to a decrease in the spin-spin relaxation time of surrounding water molecules. This change, which can be readily measured, depends on the degree of clustering and is proportional to the number of target molecules in the sample.

Miniature NMR-Chip Detects TB

As a first POC application, Weissleder and Lee are testing the device as a sensor for TB, using nanoparticles coated with antibodies against Mycobacterium tuberculosis. “The sputum smear test can detect about 10,000 bacteria per sample. Our device is 1,000 times more sensitive – we are down to about 10 bacteria per sample,” explains Weissleder, which means the device could detect many cases that the sputum smear test would miss. In addition, electronic readout reduces human bias associated with smear analysis. The microNMR device can analyze up to eight samples simultaneously in about 30 minutes and does not require skilled training to operate. A membrane filter inside the microcoil concentrates the bacteria to enhance detection sensitivity. Samples can be prepared for testing rapidly and inexpensively. “We are working with Harvard School of Public Health, and probably next year we are going to test the device in South Africa to see how it performs compared to conventional TB testing,” adds Lee.



Cancer cells in native (unprocessed) samples such as blood and biopsies are tagged with magnetic nanoparticles that bind to cancer-specific biomarkers on the cell surface. A miniaturized sensor then detects the magnetically-labeled cells through NMR. Credit: Hakho Lee

By changing the coating on the nanoparticles, the same system can be used to detect other types of infectious agents – viruses, fungi, and parasites – not only in bodily fluids but also in the environment (e.g., water supplies). The technology could have a great impact on global public health.

Profiling Cancer Biomarkers

Another line of application of the microNMR system is detection of biomarkers, characteristic substances produced by cells that reveal the molecular signature of cancer and complex metabolic disorders, such as diabetes. Weissleder’s research team currently is running a clinical trial profiling fine needle biopsy samples from cancer patients for six different biomarkers and comparing the results to conventional cytopathology. Waiting up to a week for pathology results causes anxiety in patients and delays treatment. If proven sufficiently sensitive and accurate, the portable microNMR device could be used to screen samples during the biopsy procedure. Weissleder acknowledges that the device could not be used to screen for all types of cancer: “There are certain cancers that don’t have good markers, and those we will not be able to detect,” he says.

The microNMR method will most likely be much cheaper than conventional biomarker screening. “We integrated the NMR electronics in a 2 mm x 2 mm chip. When those chips are mass produced, we can further decrease the cost of the device,” says Lee. Another potential application in the cancer arena is measuring the number of circulating tumor cells in the blood to monitor a cancer patient's response to therapy; this would allow physicians to tailor treatments to individual needs (i.e., modify the dose, stop an ineffective therapy, and switch to another treatment).

Future Directions

The team is exploring additional applications of the device, including assessing the immune status in viral infections, identifying drug targets inside the cell, and profiling subsets of white blood cells in atherosclerosis. They are screening antibodies and small molecules that can be coated onto nanoparticles to bind various biological targets. Small molecules are preferred to antibodies because they have a longer shelf life and are generally less expensive. The team also is upgrading different parts of the device and developing new magnetic nanoparticles to improve detection sensitivity and building larger arrays of microcoils for high-throughput measurements.

T2 Biosystems, co-founded by Weissleder, is developing miniature magnetic resonance diagnostic platforms for the clinic, pharmaceutical industry, home testing, environmental sensing, biodefense, and nonprofit entities. Their prototype benchtop instrument – designed for use in physicians' offices and hospital laboratories – performs a panel of diagnostic tests in less than 20 minutes. "Today, samples are sent to a central lab and results are available in 1–3 days. With this device, the results would be available in less than an hour, while the patient is still with the physician. Importantly, because of this unique technology, we would be able to take one blood sample, as small as a fingerstick, and get all of those diagnostic results. Ultimately, that fingerstick test could take place at home on a small, hand-portable device, similar to a glucose meter," explains John McDonough, CEO of T2 Biosystems.

In the future, portable magnetic resonance devices could replace existing optical techniques for rapid POC diagnostics, particularly in resource-limited settings. Thanks to its ability for fast analysis of multiple markers in native clinical samples with high sensitivity, the microNMR system could become the preferred diagnostic tool for cancer cell detection and profiling.

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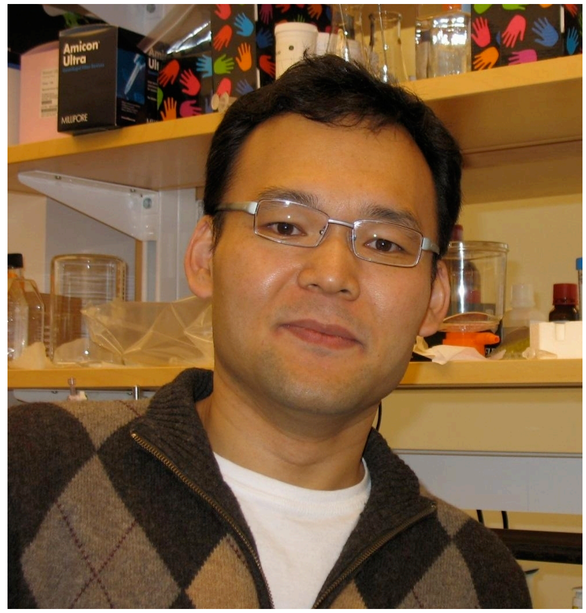

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