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Advanced Molecule Detection

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Andrew Gu, an assistant professor of biological engineering, reviews results of the work that he and postdoc Ji Wook Shim, at left, are doing with glass nanopores for single molecule detection. Gu's research on the aptamer-based nanopore sensor and its ability to detect ricin is slated for publication in Analytical Chemistry this summer. Photo by Dory Colbert

In an ongoing effort to counter potential bioterrorism attacks, federal legislators approved the Project BioShield Act in July 2004. The $5.6 billion program was designed to encourage and speed the development of antidotes to guard against biological and chemical assaults. Among the toxins frequently mentioned as a potential bioweapon is ricin, a natural poison derived from castor beans. Since no antidote for ricin poisoning exists, the best defense is preventing exposure to the toxin, according to Centers for Disease Control and Prevention public information.

Mizzou Engineering Assistant Professor Li-Qun Gu has uncovered a way to help prevent that exposure. Gu, a biological engineering faculty member who works at MU's Dalton Cardiovascular Research Center, has developed a new type of tiny glass pore that can be sized to detect the relatively large — between 10 and 20 nanometers — ricin molecule. Easily made as well as flexibly sized, Gu's nanopore forms the foundation of a technique sensitive enough to detect a single ricin molecule.

As valuable as Gu's ricin detection method may be to homeland security, he believes it's just one of many uses for his unique nanopore sensing technique. His nanopore, a wineglass-shaped tube with a hole at its base that may be as small as one thousandth the diameter of a human hair, can be

modified to detect molecules measuring anywhere from one to several hundred nanometers.

Reshaping biosensor building blocks

Gu, educated at China's prestigious Nankai University, has an interdisciplinary background that guides his approach to nanopore research. While he earned his doctoral degree in physics, Gu's studies at Nankai University included a substantial number of biological courses, and his early nanopore research at the University of Western Australia and Texas A&M built upon that biological science training.

While at Texas A&M University Health Science Center during the late 1990s and 2000s, Gu worked with proteins to develop nanopores capable of sensing the presence of a single molecule of a given material. Gu and his team successfully demonstrated that protein nanopores could be modified to serve as sensors for a variety of substances by adding a receptor molecule to the nanopore's cavity that would bind with targeted materials. The researchers found they could create sensors in this way that would detect substances ranging from HIV to TNT molecules.

Nanopore sensing works indirectly: When a nanopore fitted with a receptor in its cavity recognizes a target molecule, it chemically captures that molecule and binds it to itself. The bond between the nanopore receptor and its target molecule blocks the nanopore's hole. Researchers detect that blockage by running an electric current through the nanopore and measuring the current for minute changes that can only be caused by a bonded particle. Specifically, the current level drops when a bond exists, and resumes when the bond breaks. The frequency of the current's fluctuations also determines how concentrated those particles are. Using this technique, scientists for several years have been experimenting with feeding DNA molecules through nanopores to determine the sequence and structure of genetic components within those molecules.

But Gu realized from his Texas A&M research that nanopores made from proteins have limitations. While their sensing properties can be modified to suit a scientific task, their size cannot. Protein nanopores, which typically measure about two nanometers across, are too small to detect large molecules such as ricin. And the protein nanopore structure is fragile. In order to survive, the nanopores must be embedded in natural cellular structures called "lipid bilayers" that are sensitive to vibration and other external

conditions, making them potentially unstable.
Synthetic nanopores appear to solve those problems, but currently do not include receptors and so cannot differentiate between potential targets.

Gu's new nanpore combines the best of both. Backed by a prestigious National Science Foundation CAREER grant that runs through June 30, Gu has devised a unique and efficient technology that pairs glass nanopores with short segments of engineered DNA or RNA called "aptamers" that can recognize and bind with various molecular targets. Aptamers, typically synthesized for medical use, are ideal nanopore receptors because they can be modified to attract virtually any molecule under investigation, Gu said.

Gu credits his interdisciplinary training — and the collaborative environment that drew him to the University of Missouri in 2004 — for the inspiration that led him to merge nanotechnology with advanced biological science. Gu is awaiting the results of a patent application he filed in March 2009 for his nanopore sensor fabrication technique.

"I knew the drawbacks of protein nanopores, and I wanted to develop technology that overcomes those challenges," he said. "Aptamers are durable, and they're cheap and easy to manipulate. I've found it's a very good choice."

Hybrid benefits

Integrating aptamers with a glass nanopore provides Gu's sensors with the selectivity and sensitivity that other synthetic nanopores lack.
With aptamers serving as nanopore receptors, Gu's technique creates sensors that precisely pinpoint their targets. Only aptamers that recognize and bind to their targets with great affinity block electrical signals passed through the nanopores, giving the nanopore sensors considerable specificity. Signals that other synthesized nanopores may register when small molecules pass through their cavities are less likely to occur when both the nanopore's hole and its aptamer receptor are customized to a single target molecule, Gu said.
The aptamer's small size — typically between one and 10 nanometers — also helps make it a superior receptor while paving the way for a nanopore of the same small size, Gu said. A single captured molecule will bind to the aptamer and clearly block the tiny receptor and the nanopore in which it sits, creating an easily detectable blockage, he said
"When a target binds, its signal is more pronounced," Gu said.

A versatile tool

Having already created a nanopore detector for ricin, Gu now aims to devise a nanopore sensor that will use an aptamer to detect anthrax spores. Scientists have developed an anthrax aptamer, paving the way for a nanopore sensor, Gu said.

With a focus on bioterrorist materials because of their importance to homeland security, Gu emphasizes the potential flexibility of his invention.

His aptamer-based nanopore sensor can be used for environmental monitoring, detecting pollution or contaminating materials in water. It can be applied to medicine in many forms, in diagnoses as well as in the production of medication, Gu said. The aptamer-based nanopore can detect chiral compounds — that is, compounds with identical atom composition that cannot be superimposed on their mirror images — to ensure high concentrations of the most useful versions for medicines, he said.
“It depends on the aptamer development,” Gu said. “If the aptamer is ready, you can use it for just about anything.”

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