ANALYTICAL CHEMISTRY

Light Touch Identifies Wisps of Rogue DNA

When anthrax-laden letters contaminated a U.S. Senate building and a Washington, D.C., postal facility last fall, it often took days to get the results back from the lab. Federal officials longed for a quick and accurate detector, but "current techniques don't fit the bill," says Chad Mirkin, a chemist at Northwestern University in Evanston, Illinois. Now Mirkin and his colleagues have developed a sensitive biological assay that they hope will make other methods obsolete.

On page 1536, Mirkin's team of chemists describes an assay that, unlike more conventional methods of detecting genetic material, doesn't rely on the polymerase chain reaction (PCR) to boost its sensitivity. PCR limits a test's speed and often increases its false-positive rate. The new technique currently can detect DNA or RNA at a concentration of about 20 femtomolar: about one part in 3 trillion for an aqueous solution. That's hundreds of times better than most other methods, says Mirkin, who has plans to improve its sensitivity by another order of magnitude or two.

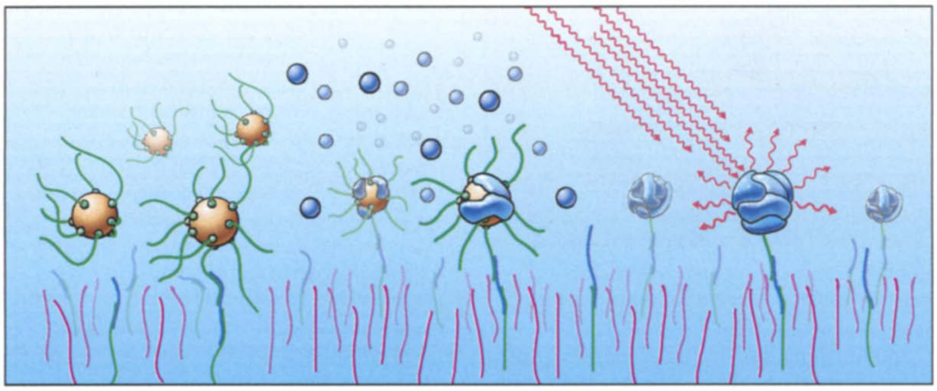
"It's a very exciting technique," says chemist Mark Wightman of the University of North Carolina, Chapel Hill. "It's a really neat and simple way to ID specific DNA and RNA fragments—and it doesn't seem to be pie in the sky."

The technique starts by making an open-face chemical sandwich out of two components, each primed to recognize a target strand of DNA or RNA. On one side is a chip covered with DNA strands, each designed to snag a fragment of the genetic material of the biological agent it needs to recognize, such as anthrax or HIV. On the other side is a set of gold nanoparticles, each also covered with DNA that will attach to a target's genetic material.

The researchers pour a solution contaminated with target substances over the chip. When the target strands bind to the complementary DNA strands on the chip, a bit of each target strand remains jutting above the forest of DNA for the treated gold nanoparticles to latch onto. Then the team soaks it in a solution of gold nanoparticles, whose attached DNA snags onto the loose ends of the target strands. By anchoring gold particles to the chip, the target strands flag their presence (see figure, below).

Ordinarily, it would be tough to detect these gold nanoparticles, especially in small concentrations. To make them easier to spot, the team tags each of them with a Raman dye, a chemical that scatters light in a distinctive way as photons make the molecule vibrate. Then the researchers expose the chip-gold sandwich to a solution of silver ions that coat the gold nanoparticles with silver, strengthening the dye's scattering properties.

When the team zaps the chip with a laser, each spot that has been exposed to the target material—the regions that are covered with silver-covered nanoparticles—scatters light.



Metal detector. In new DNA test, gold nanoparticles bind to target strands and get silver-plated. Then radiation scattered from a laser beam picks out the targets.

Different dyes scatter different colors. As a result, the researchers can test for several targets at a time, by color-coding the targets to make anthrax, say, blue and HIV yellow.

Other assays, such as those that use fluorescent dyes, can also assign different colors to different targets. But the Raman technique is more versatile, Mirkin says, offering a wider choice of dyes and scattering light over a relatively narrow part of the spectrum. That makes it easier to cram several different dye labels into the same frequency range. "We can put in 10 different dyes, giving you 10 distinct signatures" over a certain region of the spectrum, says Mirkin. "You can't do it with fluorescence. You can't even come close."

The Raman technique will have to win over biologists wedded to other methods, with cost an important consideration. But according to Wightman, the technique is ripe for the marketplace. Potential applications include use as a bioweapons sensor or diagnostic test that can be performed at a clinic rather than being sent to a lab. Mirkin has helped found Nanosphere, a company based in Northbrook, Illinois, to exploit the commercial feasibility of these nanoparticle-based techniques. —**CHARLES SEIFE**

NEUROSCIENCE

Sight, Sound Converge In Owl's Mental Map

The barn owl is a deadly hunter. Using hearing to pinpoint the scurrying of a mouse or other small animal, it swoops out of the night sky and dispatches its prey. To guide its lethal accuracy, the owl uses a mental map tuned to the location of sounds.

But this map cannot maintain itself on sound alone; it requires visual information to continually update its accuracy. But despite years of searching, only now have researchers been able to find out how those visual cues reach the map. On page 1556, Eric Knudsen and his colleagues at Stanford University School of Medicine report that they have discovered a "gate" in the brain that, when opened, allows the auditory map to receive the visual information it needs.

"The novel thing about this study is not that there is visual input into an auditory area; there are many demonstrations of that," says neuroscientist Andrew King of the University of Oxford, U.K. There have also been previous examples of gating, in which some kinds of neural input are allowed into a brain area only under certain conditions. But what makes this work "really important," says Alexander Grunewald of the University of Wisconsin, Madison, who has studied gating of sensory information in monkeys, is that this picture is more complete than others because the researchers know just how the gated information is used.

Knudsen's group showed in the early 1980s that the owl brain contains a map of auditory space in an area called the external nucleus of the inferior colliculus (ICX). Each ICX neuron responds to sounds from a certain location. The brain computes the location using differences in the timing or intensity with which the sound reaches the two ears. Knudsen's team showed in 1993 that this auditory map is modified by visual information. This is key to the map's function, says Yoram Gutfreund, a postdoc with Knudsen and lead author on the current paper, because any changes in the hearing in one or both ears—caused by changes in

ILLUSTRATION: C. SLAYDEN

Hear that? Visual signals update the barn owl's auditory map.

head size as the animal grows or hearing loss as it ages—will alter the information the brain receives. Without adjustment, the map would become misaligned, and the owl would miss its prey.

In January Knudsen's team identified a brain area called the optic tectum (OT) as the source of the visual signals that tweak the map: When the team members destroyed the connections between the OT and ICX, the map ceased adjusting. But despite the overwhelming evidence that visual signals help maintain the map, they still could not register a response in ICX neurons to visual stimuli.

Gutfreund wondered if the flow of information was somehow blocked in the anesthetized owls on which the experiments were done. He tried treating the OT with a chemical that can open up neural pathways that have been blocked by the inhibitory neurotransmitter GABA. After treatment, electrodes in the ICX began to pick up neural responses to flashes of light. The responses were specific: Just as each ICX neuron registers sounds from a particular location, each also selectively responded to visual cues from the same location. In mapping terms, that meant that the visual and auditory maps in the ICX are aligned.

Gutfreund next tricked the owls' brains to make the maps seem misaligned. Through headphones, he delivered sounds to the owls' ears that sounded as though they came from a place that was slightly offset from the location of the light. The ICX neurons responded much more strongly to the light than they had when the maps were aligned. That, says Gutfreund, is what one would expect for an instructive signal: It points out an error to be corrected.

"There are two different findings here," says Gutfreund. "The first is that visual responses can appear in the ICX, an auditory structure, but they are normally inhibited. The second is that the signals [have the right characteristics] to be the instructive signal."

With those findings, a "circle is closed," says neuroscientist Masakazu (Mark) Konishi of the California Institute of Technology in Pasadena: The researchers know where the visual information comes from and how it alters the map.

Now they are poised to answer the next round of questions. They will need to experiment on alert owls, says Catherine Carr, a neuroscientist at the University of Maryland, College Park, to learn what conditions normally open the gate for the visual signal. Grunewald offers a hint of what those conditions might be: He found in monkeys that the gating of sensory information seems to be governed by "the significance that the stimulus has in the context of the specific task," and he suspects that something similar occurs in the owl's brain.

Researchers can now also address in detail how the visual signal alters auditory neurons to bring about changes in the map. "It is becoming extremely clear that instructive error signals are going to be a major way you learn," Carr says, adding that the barn-owl example is one of the best characterized ones to date. And so the next round of experiments on the owl's auditory map is likely to have a wide audience.

–MARCIA BARINAGA

ECONOMIC ESPIONAGE

Researcher Acquitted Of Lab Theft Charge

A jury last week found a scientist at the University of California (UC), Davis, not guilty of stealing vials of a protein gel used in ophthalmological research. More serious allegations of economic espionage had already been dropped by prosecutors, who originally had accused Bin Han, a Chinese-born researcher, of planning to take the materials to China to profit from them. The case has generated widespread attention and outrage among some Asian Americans, who maintain that they are being unfairly targeted at U.S. laboratories.

Han, 40, holds a graduate degree in veterinary studies from Xian University in central China and is a U.S. citizen. He had worked in the university's ophthalmology department for 13 years until he was fired on 13 May. A week later he was arrested, jailed, and charged with theft of trade secrets, possession of stolen property, and embezzlement. Yolo County prosecutors accused him of secreting in his home freezer half of a batch of 40 vials of protein gels used in cornea-transplant research that were owned by the university, with the intent of taking them to China for profit. Investigators also found a one-way plane ticket to China.

Legal victory. Bin Han with court documents asserting his innocence.

Han maintained that he had picked up the gels from a nearby company and had simply not delivered all of them to his lab when they were discovered in his home, where he lives with his wife and two children. He also said that he was planning to visit his ailing mother in China and that the ticket was open-ended, not one way. The charges eventually were reduced to a single misdemeanor charge of petty theft and embezzlement after his attorneys showed that the gels were readily available in China and that they had been provided without charge to the university, making them worth less than the $400 minimum for a felony charge.

The case has drawn the ire of many Asian Americans, including California state legislator Judy Chu. "I am distressed by the similarities between Dr. Han's case and that of Dr. Wen Ho Lee," the Los Alamos National Laboratory physicist who was charged with stealing classified material, Chu wrote in an 18 July letter to UC Davis Chancellor Larry Vanderhoef. "Cases such as those of Dr. Lee and Dr. Han further perpetuate the misconception that Asian Americans cannot be trusted, are not loyal to the United States, and pose flight risks, simply for being of Asian heritage."

Han says that he may fight to get his job back. The university told him it was terminating his contract because he did not provide the necessary supervision to a graduate student, Han says, but he claims that the real reason was his refusal to allow a senior researcher to claim credit for work done solely by Han. "I argued with him, and he got very mad," Han said.

University officials declined to discuss the reasons for Han's firing, but they said the university is looking into the grievance he has filed. "The university is committed to conducting a thorough review of this grievance and reaching a fair and equitable resolution," says campus counsel Steven Drown. Drown says that the university might also conduct an in-house "administrative review" of the issues raised in the criminal trial.

–ANDREW LAWLER

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