DNA nanosensors pave way for cancer tests, drugs

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Custom DNA molecules can be used to make sensors that can quickly detect a broad class of proteins – and could be used to personalize cancer treatment and even to monitor the quality of stem cells.

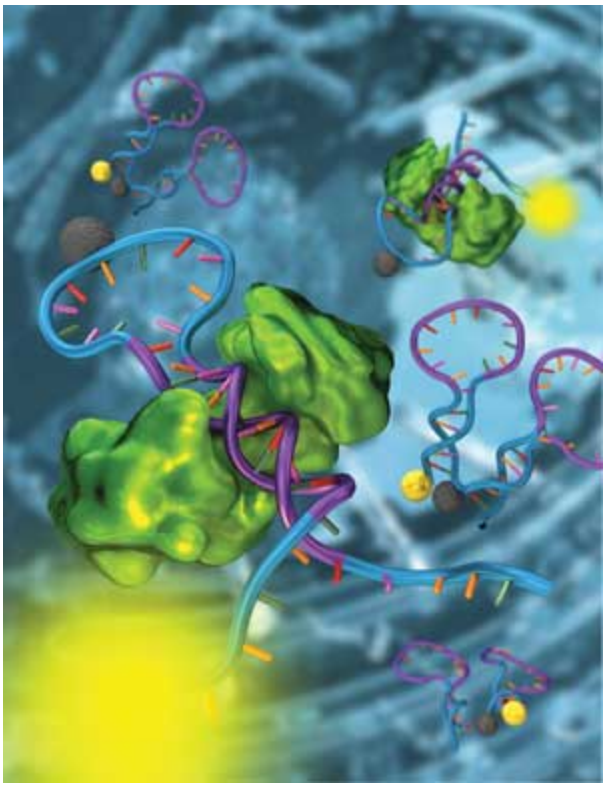
Researchers from the University of California, Santa Barbara (UCSB), and the University of Rome Tor Vergata developed the new nanosensors, which monitor the activity of proteins called transcription factors, then read the genome and translate it into instructions for synthesizing the various molecules that compose and control the cell. This information could determine which transcription factors in a patient's cancer cells are activated or repressed, enabling physicians to prescribe the right combination of drugs for each patient, according to Alexis Vallée-Bélisle, a postdoctoral researcher in UCSB's department of chemistry and biochemistry.

Andrew Bonham, a postdoctoral scholar at UCSB and co-first author of the study, explains that the team's approach to reading transcription factors is quick and convenient. By adding their sensors to the mashed-up cells, they can measure the sample's level of fluorescence.

Alexis Vallée-Bélisle (left) and Andrew Bonham (right). Courtesy of George Foulsham, Office of Public Affairs, UCSB.

The international research effort – organized by senior authors Kevin Plaxco and Francesco Ricci – started when Ricci realized that all of the information necessary to detect transcription factor activities is already encrypted in the human genome and could be used to build sensors. Once activated, each of the thousands of different transcription factors can bind to its own specific target DNA sequence, he explained. These sequences were used as the foundation for building the nanosensors.

The key to the technology came from studies of the natural biosensors inside cells. The scientists expounded upon the fact that all creatures monitor their surroundings with biomolecular switches composed of RNA or proteins, which are small enough to operate inside a cell and could work in complex environments. Inspired by the efficiency of these natural nanosensors, the researchers teamed with professor Norbert Reich of UCSB to build synthetic switching nanosensors using DNA rather than proteins or RNA.



A structure-switching nanosensor made from DNA (blue and purple) detects a specific transcription factor (green). Using these nanosensors, researchers have demonstrated the direct detection of transcription factors in cellular extracts. They believe that their strategies will allow biologists to monitor the activity of thousands of transcription factors and will lead to more efficient cancer testing and medications. Courtesy of Peter Allen.

Specifically, they re-engineered three naturally occurring DNA sequences, each recognizing a different transcription factor, into molecular switches that become fluorescent when they bind to their intended targets. Using these nanosensors, the researchers can determine transcription factor activity directly in cellular extracts by measuring their fluorescence level. The work was described in an online article published Aug. 4 in the *Journal of the American Chemical Society* (doi: 10.1021/ ja204775k).

This strategy ultimately will allow biologists to monitor the activation of thousands of transcription factors, leading to a better understanding of the mechanisms underlying cell division and development. The nanosensors could also be used to screen and test new drugs that could inhibit the transcription factor binding activity responsible for tumor cell growth.

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