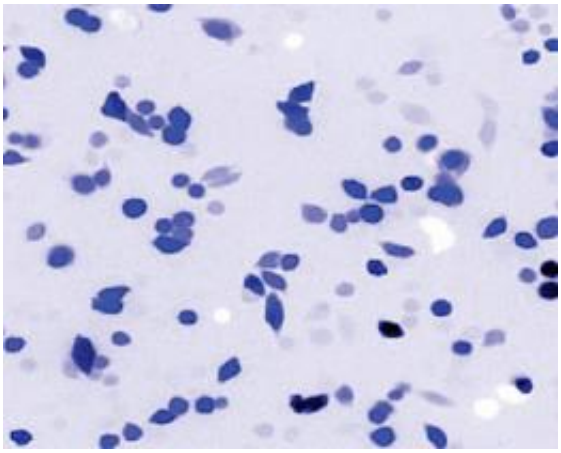
Study adds timing capability to living cell sensors

February 8 2012, By Laura Ost



Micrograph of human cells modified to act as metal sensors. Researchers at JILA built hardware to help time the dynamic states of these sensors, which change fluorescence color when they bind metal ions. The cells are false-colored to indicate the extent of their reactions; the darker cells have bound the most metal ions. Credit: Hairong Ma/JILA

(PhysOrg.com) -- Individual cells modified to act as sensors using fluorescence are already useful tools in biochemistry, but now they can add good timing to their resumé, thanks in part to expertise from the National Institute of Standards and Technology (NIST).

With the added capability to track the timing of dynamic biochemical reactions, cell sensors become more useful for many studies, such as measurements of protein folding or neural activity.

As described in the *Journal of the American Chemical Society*, a NIST biophysicist working at JILA and a collaborator at the University of Colorado Boulder (CU) developed a microfluidic system that records biochemical reactions over a time span of milliseconds to seconds in living human cells modified to act as FRET (fluorescence resonance energy transfer) sensors.

The fast, flexible system uses lasers to measure sensor signals at two points in time at a rate of up to 15 cells per second. Statistical data, such as the average value of the FRET response for thousands of cells, can be collected in minutes.

"Our system is the first one that measures FRET response times at the single-cell level, while at the same time measuring over many cells," says JILA Fellow Ralph Jimenez, whose research group built the optics, microfluidics, electronics and other hardware.

JILA is a joint institute of NIST and CU. Jimenez is collaborating with Amy Palmer, an assistant professor in CU's Department of Chemistry and Biochemistry, who handled the molecular design and cell-biology aspects of the project.

The FRET technique relies on reactions that occur between large biological molecules in close proximity to each other. One molecule absorbs light energy from a laser and transfers this energy to the nearby acceptor molecule. The acceptor molecule then releases this energy as light (fluorescence) at a characteristic wavelength that is different from the original laser light. Measurements of this fluorescence indicate the extent of the energy transfer. FRET can be used to study many types of cellular processes. In these experiments, the researchers were interested in the type and concentration of metal ions within cells, which can affect important cell processes. The JILA/CU experiments used cells genetically modified to take up particular metal ions and signal changes

in their concentrations by altering the FRET signals.

The researchers made a microfluidic device with a flow-control valve system that mixes cells and metal-containing chemicals in just a few milliseconds. The cells then pass single file through two blue laser beams that excite the FRET fluorescence signal at different locations in the device. With precise flow control and flexible device design, cell travel time between the two locations can be varied from 1 millisecond to 10 seconds. Scientists measure the FRET signal changes within individual cells between the two locations.

"FRET is an important measurement technique used in bio-imaging, so it's great that NIST could begin to contribute to measurements of the fidelity of FRET-based sensors," Jimenez says. "We have a lot more work planned for the future with this instrument."

The project is part of the research team's effort to develop cell sensors with improved optical, physical and chemical properties and to enable detection of very faint signals in living cells. The work was supported in part by a CU-NIST seed grant, the National Institutes of Health and the National Science Foundation.

More information: H. Ma, et al. High-throughput examination of FRET-detected metal-ion response in mammalian cells. *Journal of the American Chemical Society* (JACS). Published online Jan. 19, 2012. (Communication) DOI: 10.1021/ja2101592

Provided by National Institute of Standards and Technology