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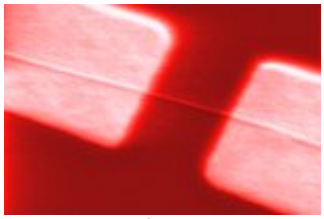
Nanowire sensor could help drug discovery

23 February 2005

Researchers at Harvard University, US, have created a silicon nanowire device that can detect interactions between small molecules and proteins. The system could have applications in drug discovery.


Nanowire sensor

"We have been working on biosensing with nanowire detectors for some time, and were asking whether this 'field-effect' device could be adapted to label-free, real-time detection of small organic molecules, since these play important roles in biological systems for signalling and more generally as drugs," researcher Charles Lieber told *nanotechweb.org*. "For the first time [we demonstrated] very general, real-time, high-sensitivity detection of small molecule binding/inhibition in biological systems."

Lieber and colleagues used their silicon nanowire device to investigate the effects of various molecules on the binding of ATP to the tyrosine kinase Abl. They linked Abl molecules to the surfaces of the silicon nanowires and introduced the test solutions in microfluidic channels surrounding the sensor.

When ATP was added to the sensor, the ATP bound to the Abl molecules. Since ATP is negatively charged, this increased the conductance of the nanowire field-effect transistor, in the same way that a negative gate voltage would.

In turn, introducing molecules of the drug Gleevec (STI-571) inhibited binding of ATP to Abl and reduced the conductance of the device. Gleevec is used as a treatment for chronic myelogenous leukaemia, a disease linked to tyrosine kinase. But Gleevec may be unable to treat the leukaemia when mutations in the kinase have occurred. That's why scientists are looking for additional inhibitors of ATP or substrate protein binding to tyrosine kinases.

The team used their detector to rank the ATP binding inhibition performance of four additional small molecules. Their results agreed with the ranking of inhibition constants reported by others, although values were not available for all the molecules.

"The technique provides much higher sensitivity - several orders of magnitude - than other label-free techniques such as surface plasmon resonance (SPR) and calorimetry," said Lieber, "and it is certainly much easier to carry out compared to tests involving the transfer of radioactive phosphorous (from ATP) to the enzyme substrate and subsequent counting."

According to Lieber, the method also requires much smaller amounts of proteins than other methods, which could be critical for studies of new kinases that aren't yet efficiently produced and the general economics of larger scale drug discovery. "Our work can be extended directly in many other important directions, such as studies of protein-protein interactions and how these are modulated by small molecules (drugs) - an area central to proteomics," he said.

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Now the team is working to create larger arrays of sensors that can simultaneously screen different molecules or proteins. "For example, we can now routinely make arrays containing tens of working sensor devices and have developed methods for immobilizing distinct surface receptors in regular patterns within the array, thus enabling simultaneous detection of different molecules/proteins," said Lieber. "We are interested in pushing these arrays by several orders of magnitude in size, which will require advances in several areas of nanoscience but have great potential payback."

The researchers reported their work in *PNAS*.

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