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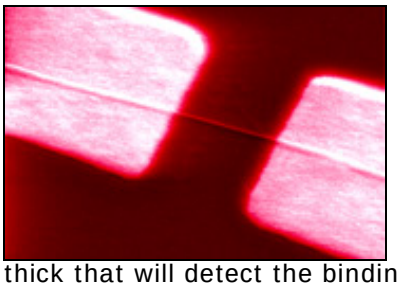
Nanowire sensors pass drugs test

Detecting the binding of small molecules to proteins is a central element of the search for new drugs. Sensors made from silicon nanowires can take the search to new levels of sensitivity.

Philip Ball



Screening 'libraries' of molecules to find new drug candidates could be made cheaper and quicker by using arrays of nanowire sensors, researchers at Harvard University have shown.

They have created electronic sensors from silicon wires just a few tens of nanometres thick that will detect the binding of a small molecule to a protein[1]. The sensors can measure how effective various molecules are at inhibiting the binding between a protein and the molecule it is 'designed' to accommodate (called the substrate).

Many drugs act as inhibitors of this sort. By switching off the protein-substrate interaction, they can cut a molecular-signalling pathway that leads to the onset of disease. The early stages of drug discovery are typically concerned with identifying potential inhibitors of proteins.

Charles Lieber and his co-workers at Harvard have found that their silicon nanowire devices can spot the way a small drug molecule with the trade name Gleevec inhibits the binding of adenosine triphosphate (ATP) to a so-called tyrosine kinase enzyme called Abl. ATP 'switches on' Abl, a process that seems to be involved in the development of a type of leukaemia. So in other words, the nanowire sensor would identify Gleevec among a collection of other small molecules as a promising drug candidate for treating this form of the disease.

Nanowire sensors are currently one of nanotechnology's most promising products for biomedical research[2]. Lieber's group has previously shown that such devices can detect the binding of proteins to their substrates[3] and the sequence-specific pairing of strands of DNA[4], which is a critical facility for genomics research. The devices are extremely sensitive — they can detect very low concentrations of their target molecules, in principle being able to register the binding of a single molecule.

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The sensors are basically transistors that are 'switched' on or off (that is, between a high-current and low-current state) not, as in normal transistors, by applying a voltage to one of their electrodes, but by the binding of a molecule to their surface. A transistor is switched by altering the density of charge carriers in a conductive channel between the input ('source') and output ('drain') terminals. In a nanowire transistor, this channel is the semiconducting wire itself, which is electrically connected by metal contacts at each end.

If a molecule bearing electrical charge gets stuck to the nanowire surface, this causes charge carriers either to accumulate or to be depleted within the wire, depending on whether the charge on the bound molecule and on the charge carriers is of the same or of opposite sign. That leads to a change in conductance through the wire, so the binding event is registered as a change in the current passing through the device. The nanoscale dimensions of the wire are crucial — because they are so thin, accumulation or depletion of charge carriers happens more or less throughout the entire thickness of the wire.

Lieber and colleagues used silicon wires grown by chemical vapour deposition on catalytic nanocrystals of gold. They were doped with boron so that they contain positive charge carriers (holes), and the researchers deposited titanium/gold contacts at each end. To turn these devices into sensors that detect the binding of Abl to ATP, they tethered Abl proteins to the wire surfaces by covalent chemical bonds. ATP has a negative charge, so when ATP binds to the Abl molecules on the surface, this creates an accumulation of charge carriers in the wire and an increase in its conductance. In this way the researchers were able to sense ATP binding at concentrations as low as 10^{-10} M (100 picomolar).

Gleevec can plug Abl's binding site and prevent ATP from sticking to it. But Gleevec has no electrical charge, and so if this molecule inhibits ATP-binding, it prevents the current-boosting effect. Lieber and colleagues were able to use the size of this effect to calculate the binding constant between Abl and ATP (a measure of the strength of binding) and the corresponding 'inhibition constant' of Gleevec.

That quantitative information is important, because it enables the effectiveness of a range of inhibitor molecules to be assessed. The researchers compared Gleevec with three other small molecules with similar chemical structures, and found that it out-performed all of them. Combined with a microfluidic system for guiding solutions of different candidate molecules to different sensors, this scheme could enable large libraries of molecules to be screened simultaneously and the most effective candidates to be identified for further testing as drugs.

At present, this kind of screening usually requires that the candidate molecules be labelled, for example with fluorescent tags, so that their binding to the target proteins can be spotted. The need for labelling makes the screening process cumbersome. There are other label-free techniques available already, but Lieber and colleagues think that their nanowire sensors have some important potential advantages.

In particular, they require only tiny amounts of each candidate compound, and the devices can be incorporated into vast detector arrays mounted on a silicon chip for quick and convenient automated testing of molecule libraries. One of the rival methods, called surface plasmon resonance spectroscopy, lacks the very high sensitivity that permits such small quantities of material to be used, although currently it does furnish rather more quantitative information about the kinetics and thermodynamics of the binding process than the nanowires can supply — information that may be very useful for understanding the chemical interactions and making rational use of them in drug design.

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