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By Julia Karow

UK-based Oxford Nanopore Technologies has started a research and development group in the US that will focus on solid-state nanopores and detection methods, *In Sequence* has learned.

The move follows several years of collaborations with solid-state nanopore researchers at Harvard University. Oxford Nanopore's first US employee, Ping Xie, a former postdoc at Harvard, recently published a report on a novel nanopore detection method that combines nanowire field effect transistors with solid-state nanopores and promises high speed and integration density.

Xie, who joined Oxford Nanopore last month, is currently its only US-based researcher and still works out of Harvard, but the company plans to grow the group over time and has just incorporated a US subsidiary "to accommodate the growing number of employees we expect to employ in the US," according to a spokesperson for Oxford Nanopore.

Oxford's US group will work on field effect transistor-based sensing approaches for single molecules that "may have significant speed advantages," she said. The group will explore a variety of methods and materials, including nanowires and graphene.

While the company is not disclosing the size of its investment in the new US branch, the spokesperson noted that it has had strong ties with Harvard for several years, including exclusive licensing agreements for nanopore technologies, research support for Harvard labs, and regular visits between Harvard researchers and Oxford's UK team.

In 2008, Oxford Nanopore signed an agreement with Harvard that gave it exclusive rights to develop and commercialize solid-state nanopore sensing methods developed by Daniel Branton, George Church, and Jene Golovchenko at Harvard and their collaborators David

Deamer and Mark Akeson at the University of California, Santa Cruz, as well as John Kasianowicz at the National Institute of Standards and Technology. As part of the license, Oxford Nanopore agreed to support fundamental nanopore research at Harvard with an undisclosed amount of funding (*IS 8/12/2008*).

Last March, the company added another license from Harvard, giving it exclusive rights to develop and commercialize graphene technology for DNA and RNA analysis from the labs of Golovchenko, Branton, and Charles Lieber (*IS 3/15/2011*).

Internally, Oxford Nanopore has so far mostly focused on a biological nanopore, a variant of the alpha-hemolysin protein, and has built a general nanopore-based platform for the analysis of nucleic acids, proteins, and chemicals, called the GridIon system.

For DNA sequencing, it has been pursuing both an exonuclease approach, in which an enzyme feeds individual nucleotides into a protein nanopore, and strand sequencing, in which an intact DNA strand passes through a nanopore. For exonuclease sequencing, it has a commercialization agreement with Illumina.

While the company is tight-lipped about its commercialization plans, it is currently recruiting early-access collaborations managers for DNA sequencing, a vice president of manufacturing and operations, and a vice president for sales and marketing.

Nanowire-Nanopore Sensors

In a paper published online in *Nature Nanotechnology* last month, Oxford Nanopore's Xie and his Harvard colleagues described how they combined solid-state nanopores and silicon nanowire field effect transistors to create a sensor that measures local voltage changes that occur when DNA moves through the pore.

According to Xie, until recently a postdoc in Lieber's lab in the department of chemistry and chemical biology at Harvard, this is a new general detection method that could work with any type of potential-sensitive sensor, not only nanowire FETs.

Because the signal is roughly proportional to the ion current that passes through the pore, the new method can take advantage of previous nanopore developments that have measured changes in ion current — the detection method used by Oxford Nanopore so far — such as methods for base differentiation, he said. This is in contrast to other novel detection methods, for example those based on tunneling, for which base identification methods need to be developed from scratch, he added.

One of the main advantages of the new method, which requires an ion gradient, is that the signal is highly localized, so there is no cross-talk between nanopores. This means that it could be used to integrate millions of nanopores and transistors on a single chip, which Xie said is not possible with the present ion current detection method.

Further, the FET signal is quite large, in the micro-amp range, compared to the nano-amp or pico-amp signals from ion current or tunneling detection, and it is also very fast, he said.

Fabrication methods for the FETs are "totally compatible with current silicon technology," according to Xie, so he and his colleagues can take advantages of many developments of the semiconductor industry.

While the development of base recognition by a single nanopore could be likened to the invention of an individual transistor, "our work can integrate millions of them together; it's more like the invention of the integrated circuit," he said.

Xie and his co-workers have not yet shown that they can use their FET sensor to distinguish between DNA bases. In order to do so, they would need to "find a suitable base differentiation reading head that can be integrated with this," he said. Also, to sequence DNA at high throughput, they need to develop "all kinds of circuitry and readout electronics to read the high-density array data."

But because the base recognition technology "is more or less there," this could be achieved in "a few years," he said, depending on the resources available.

At Oxford Nanopore, Xie will work on a number of projects in collaboration with his Harvard colleagues, including the FET-based detection technology described in the paper. One idea is to switch over to graphene, which has advantages because it is very thin, enabling single-base resolution, and because the conductance across a graphene membrane is large, providing for high detection bandwidth, he said.

Recently, Oxford Nanopore has started to face competition in the nanopore detection space: Genia, based in Mountain View, Calif., which is backed by Life Technologies, said that is has developed its own semiconductor chip platform to measure arrays of biological nanopores (see article, this issue).

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