Next-generation sequencing

The speed, cost and accessibility of DNA sequencing has been transformed in recent years by new technologies, opening up exciting possibilities for disease diagnosis and therapeutic intervention. This month, we interview two of the pioneers in the field.

Daniel Branton, Ph.D.
Emeritus Professor of Biology, Harvard University, Boston, Massachusetts, USA.

In 1991, a conversation with a friend and collaborator, David Deamer, about the push to sequence the human genome catalysed Daniel Branton's entry into the field of sequencing technologies. "Both of us felt that there had to be better ways of undertaking such a giant sequencing task than with clumsy, slow gels, and each of us had alternative suggestions," recalls Branton. "But when David proposed driving a strand of DNA or RNA through a nanopore to determine how the nucleobases modulated the ionic current through the pore, we both thought it might provide an ideal route to sequencing."

Having spent much of his career as a cell biologist (since becoming Professor of Biology at Harvard in 1973) investigating cell membranes and their interactions with the cytoskeleton, Branton thought that trying such experiments would be a refreshing new research endeavour. Since then, Branton and Deamer (who is a professor at the University of California, Irvine, USA) have continued their research in trying to derive sequence information from nanopores, and have been joined by many of their students and other investigators. "Although early nanopore experiments disappointed naive expectations of an easy path to inexpensive DNA sequencing, much progress has been made," says Branton (see *Nature Biotech.* **26**, 1146–1153; 2008). "And the advantages of nanopore sequencing — which offer the prospect of sequencing a mammalian genome for ~US$1,000 in ~24 hours — are so attractive that I continue to address the new challenges in nanopore research."

Tackling these challenges has taken Branton's research in many directions, including molecular biology, biochemistry, physics, electronics, material science and engineering. Consequently, he has had to become familiar with many new methods and ways of thinking. "Fortunately, one of my most valuable career experiences was to learn early on not to be timid about trying new methods about which I knew little," says Branton. A collaboration in the 1960s with Deamer demonstrated the applicability of Branton's proposal that freeze-etching methods for electron microscopy could reveal the internal structure of biological membranes (*Science* **158**, 655; 1967), much to the surprise of experts in the techniques. "Indeed, following a lecture on these results, one expert asked what specialized facilities I had used," Branton says. "On hearing that we had only some makeshift equipment on a bench-top, he laughed and said: 'Dan, if you had known more about what you were doing, you would have realized that you cannot get any results doing the experiment the way you did!'"

Now, together with Jene Golovchenko, Professor of Physics at Harvard, Branton guides the research of a group of about 18 people with training in molecular biology, biochemistry, physics, electronics and material science. He finds it particularly rewarding to know that their interdisciplinary research could result in rapid improvements in disease intervention, drug discovery and treatment selection. "I also find it thrilling that the notion of sequencing by threading a DNA molecule through a membrane channel — an idea that was at first labelled as 'wild' — is now taken seriously and is stimulating excellent new science in many other laboratories," he concludes.

Jonathan Rothberg, Ph.D.
Chairman, Chief Executive Officer, Ion Torrent Systems, Guilford, Connecticut, USA, and Chairman, RainDance Technologies, Lexington, Massachusetts, USA.

During his undergraduate engineering courses at Carnegie Mellon in the mid-1980s, Jonathan Rothberg realized that the decoding of the human genome was a coming revolution. "DNA sequencing was unleashing an explosion in understanding, and so I became very interested in the impact it could have on life sciences," he says. This started him on the course to founding 454 Life Sciences, which developed the first commercial product for next-generation sequencing.

Rothberg was also intrigued by how the mind works, and so did his graduate research in molecular biology with Spyros Artavanis-Tsakonas at Yale, Connecticut, USA, where he applied DNA sequencing to discover a gene called *slit* that was important in the *Drosophila melanogaster* nervous system. But he did something much more unusual for a graduate student as well: founding CuraGen, one of the first genomics companies.

"I wanted to apply what I had learned to health care, but I was in a fantastic lab, and it was expected that I would be an academic," says Rothberg. "Luckily, I discussed starting a company with Lynn Jelinski, who ran the biotechnology centre at Cornell [New York, USA], and she said: 'Why don't you just do it?', and so I did. We wrote grants and a business plan for a company that would use computers and sequencing to discover drugs based on human genomic information, and we got the funding." Less then a decade later, CuraGen had 500 employees and a market capitalization of US$5 billion. CuraGen also published the first global proteomics maps of living organisms and brought some of the first genomics-based drugs into the clinic.

In 1999, Rothberg's career had another key turning point. "When my son was born, he was rushed to the intensive care unit. At that moment, I realized I wanted to make drugs based on an individual's genome and needed to miniaturize sequencing." On his paternity leave he came up with the ideas behind 454 Life Sciences, which developed the first massively parallel sequencing platform, dramatically reducing the cost of sequencing. For example, the technology was used to sequence the first individual human genome — James Watson's — at a fraction of the cost of the first human genome: $1 million rather than $1 billion (*Nature* **452**, 872–876; 2008).

Continuing his drive to develop new technologies, Rothberg co-founded RainDance Technologies in 2004 to enable miniaturization of a wide range of laboratory methods. After 454 Life Sciences had been acquired by Roche in 2007, he founded Ion Torrent Systems to make sequencing accessible to all, by pioneering a novel approach leveraging a semiconductor device to directly translate chemical sequencing information into digital data rather than using light as an intermediary, as in standard methods. "We want high-throughput sequencing technology to be so low-cost to buy and use that it becomes ubiquitous, so we developed an electronic chip to do it, much like the microprocessor did for computing," he says.

Overall, Rothberg emphasizes that it is possible to pursue outstanding science in industry. "We have demonstrated that you can do influential, and transformational research at companies, from decoding the Neanderthal Genome, to uncovering what was killing the Honeybee. My love is science; I just do it in a different context."