



Photo: BGI

So far, Chinese genomic research is carried out with Western instruments (pictured above the Beijing Genomics Institute's armada of 28 Illumina Genome Analyzers). This, however, could undergo a radical change from 2013 on.

Roche GS FLX DNA sequencers that are used for the Mammoth Genome Project being conducted at the Center for Comparative Genomics and Bioinformatics at Pennsylvania State University. Currently, a high-resolution sequence of the woollen animal's genome with more than 4 billion base pairs is being determined there.



Photo: Pennsylvania State University

Chinese to develop sequencing device

Eastern Giant Arising?

Is next-generation sequencing really a money spinner, or is it just a sexy but, commercially, marginal thing? A Chinese venture pins its hopes on the first alternative – and is planning on doing something big.

What's the real value of the worldwide genome sequencing business? Unfortunately, most manufacturers and sequencing service providers refuse to disclose their financial figures, while market surveys aren't worth the enormous sums that the market research bureaus request for reading tea leaves. Is the industry really putting its bets on a technology that yields adequate profit in the long term? In light of their pushy (and expensive) propaganda campaigns, instrument manufacturers and sequencing service providers should be keeping their fingers crossed.

Admittedly, the few figures available would lead one to assume that the sequencing business is, at least, profitable. Company officials at Roche, for example, recently disclosed that their sequencing business doubled in 2008, while growing slower with just additional 12% in 2009. Roche's main rival from the USA, Illumina, grew with a similar 15% within 2009, yielding revenues of €460 million and a net income of €35 million.

Great white commercial hope

Anyway, it is all but certain that third-generation sequencing is a great white commercial hope. There are three major technologies to investigate genomes – microarrays, real-time PCR and sequencing. In recent years, the latter has made by far the most technological progress, beginning in 2005 with the first commercially available “next generation” sequencing device. 454 Life Sciences' GS20 sequencing machine then used a novel, massively parallel sequencing-by-synthesis approach. With-

in a few years, next generation sequencing has largely displaced the traditional Sanger capillary sequencing technology.

Even a related, highly acclaimed technology like DNA microarraying is seriously impinged by the novel sequencing methods. Next-generation sequencing is regarded as the biggest change in genomics since the introduction of the microarray technology. Some even believe that microarrays could become redundant in many applications if sequencing costs continue to drop in the future.

Three major players and a new kid

As far as the equipment is concerned, three companies currently compete with their pricey devices. Illumina (located in San Diego, California) is the market leader with its Genome Analyzer II systems (previously known as Solexa) with Roche/454 (Basel, Switzerland) and Applied Biosystems/SOLiD (Carlsbad, California) following close behind with their own tricky gadgets. While outrider Roche/454 provides the longest reads at the highest cost per megabase, Applied Biosystems/SOLiD currently offers the lowest priced sequencing.

Anyway, most market mavens estimate that Illumina's technology will dominate the market for the next three years.

A fourth competitor, Helicos Biosciences from Cambridge, Massachusetts, has been challenging the triumvirate since late 2008 with its “Heliscope Single Molecule Sequencer” that enables considerably higher throughput rates than existing technologies. It's still too early for a reasonable forecast as to whether Helicos will rise to become serious competition for the top dog trio.

Additional players are lying in wait. Most of them also focus on single-molecule sequencing technology, such as Pacific Biosciences (located in Menlo Park, California); they are due to launch their novel device in the second half of 2010.



A completely different approach is used by Oxford Nanopore Technologies, a new UK company that has developed a label-free nanopore-based sequencing method. Based on work by the Oxford University professor Ha-



Photo: Oxford Nanopore Technologies

Oxford University professor Hagan Bayley has developed a completely new sequencing approach, working purely by electrical detection.

gan Bayley, it requires little sample preparation and no optical readout. "It works purely by electrical detection," Bayley confirmed in an interview. Individual bases are cleaved off by an exonuclease and pass through a modified protein nanopore, where each type of base blocks the ion current across a lipid bilayer to a different degree, allowing them to be identified by different current flows. A presentation by Oxford Nanopore predicts that, "The basic sequencing process may be scaled up dramatically".

In early 2009, even the established player Illumina invested €12.5 million in the British startup. If Oxford's nanopore technology lives up to the promise of its inventor Bayley, who was named "Entrepreneur of the Year" in 2009 by the Royal Society of Chemistry, Illumina will be thrilled about the exclusive rights for marketing, sales, distribution and service.

Competitors aren't twiddling thumbs

One can be sure that Illumina's competitors aren't twiddling their thumbs. Indeed, not so long ago Applied Biosystems invested an undisclosed sum in another premature nano-sequencing platform being developed by Visigen Biotechnologies. This spin-off from the University of Houston, Texas, was founded in 2000 by the former Professor of Biology and Biochemistry, Susan Hardin. Visigen works on, "a massively-parallel, single-molecule sequencing system that is capable of sequencing a human genome in less than a day for \$1000" (equivalent to €700).

The company's technological clou is sophisticated: they engineer both polymerase and nucleotide triphosphates to act together as direct molecular sensors. In so doing, signals on DNA base identity can be detected in real-time from single molecules. Har-

din affirms that sequencing rates of 1Mb/sec/machine are realistic.

Attack from the Far East

Meanwhile Far East tradesmen are also greedy to enter the sexy sequencing business. In December last year, the Beijing Institute of Genomics (BIG), a subsidiary institute of the Chinese Academy of Sciences, announced a joint venture with the Inspur Group (a Chinese computer technology company) to develop a third-generation genome sequencing device. It is advertised as "slashing the cost of genome sequencing by 99 percent", while being able to sequence a person's genome in an hour at a cost of \$1000 (€700).

Yu Jun, Vice Director of BIG, announced that, "the first test instrument is expected to be available in 2013". The made-in-China instrument will help the country get a leading edge in the field, Yu added.

Indeed, the "ppb" (price per base) seems, at present, to be the bottom line. With less regard to quality, the top dogs are feverishly working to improve their devices' performances. While the cost of the first human genome's sequencing once amounted



Photo: BIG

Officials from the Beijing Institute of Genomics and from the Inspur Computer Group sign a treaty for the development of a 3rd-generation sequencer, "expected to be available by 2013".

to roughly €2.1 billion (the publicly funded "HGP" project) or rather €210 million (Craig Venter's Celera project), the current price for decoding a whole human genome dropped down to €35,000 at the end of 2009. According to market mavens, this sum will fall to €3,500 by the end of 2010 and, to €700 in 2014 at the latest

Service providers as the lucky winners?

Whatever you purchase for your lab, whether it's Illumina's Genome Analyzer II, Roche's Sequencer FLX or Applied Biosystems' Solid 3 Plus system, next-generation sequencing devices are tremendously expensive. To boost the distribution of their own platforms, Illumina, Roche and Applied Biosystems usually offer their cus-

tomers high discounts on the standard prices. It's exactly the same trick as with inkjet printers: the manufacturers under-price their devices and make their money with pricey bits and bobs (aka consumables), the



Photo: GATC Biotech

GATC's CEO, Peter Pohl, controls, "the largest commercially available sequencing capacity in Europe".

attractive margins are generated with accessories, kits, reagents, tubes, spare-parts and support.

To keep control on their expenditures, more and more companies thus abandon in-house sequencing and outsource their sequencing projects. This has cleared the way for service providers such as GATC Biotech (Constance, Germany). GATC, founded in 1990 and still privately owned by the Pohl family, characterises itself as "Europe's leading service provider of DNA sequencing". With over 10,000 customers in 40 countries and offering all the leading sequencing technologies by Illumina, Roche/454 and Applied Biosystems, GATC has the largest commercially available sequencing capacity in Europe with two terabases per year.

European-American venture

To strengthen its market position, GATC has recently joined up with its competitor Complete Genomics (CG) from Mountain View, California. CG is to sequence and assemble the genomes and provide GATC with SNPs and similar detected variants. GATC will then perform additional bioinformatics analysis and refine the data.

Using its own proprietary sequencing technology, called "cPAL" (combinatorial probe-anchor, using billions of DNA nanoballs immobilised on a slide), CG especially addresses pharmaceutical and biotech companies that don't want to invest in their own sequencing equipment. At the moment, CG is building "the world's largest commercial human genome sequencing center", according to a press release, "having the capacity to sequence ten thousand genomes in 2010".

Well, the newcomers from Beijing will have to look sharp, or they'll miss the boat.

WINFRIED KOEPELLE