SOUL OF THE NEW GENE MACHINES

Building DNA chips using tricks from nanotech and bioinformatics, a startup aims to cash in on the genomics revolution. **BY STUART F. BROWN**

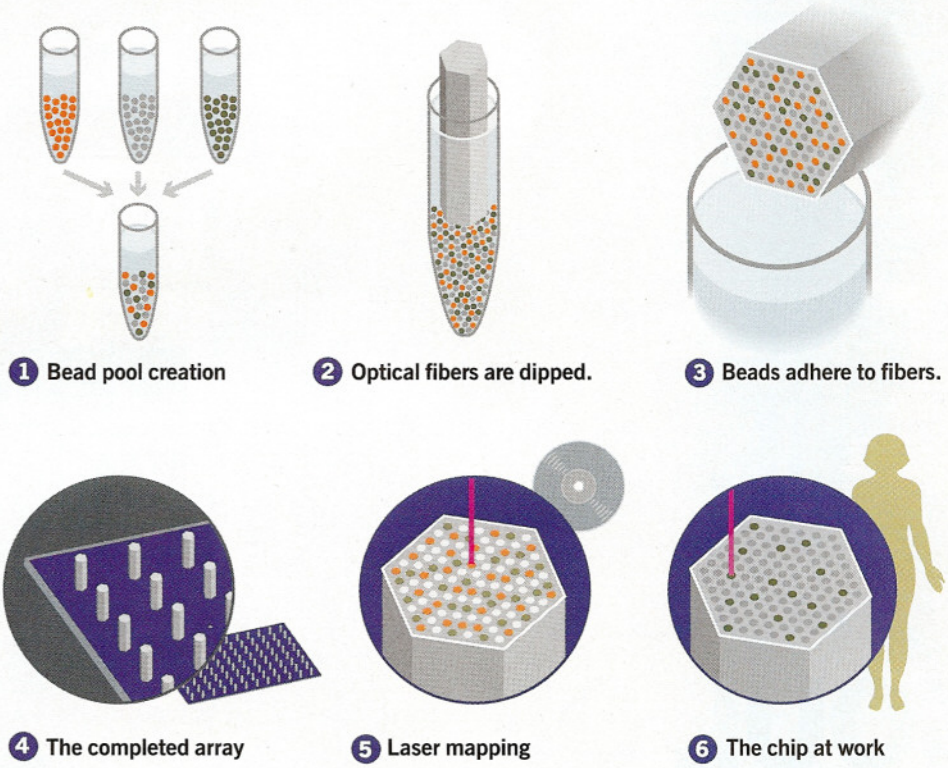
THIS IS MODERN MEDICINE'S MILLION-DOLLAR question: Does a given human's DNA—yours, for instance—contain a mutation that researchers know or suspect is related to disease? One of many firms setting out to answer it is Illumina, a San Diego biotech. In its lab an army of high-performance machines whimsically called Oligators synthesize zillions of short, single-stranded fragments of DNA known as oligonucleotides, or oligos. Although most of the oligos are only about 17 nanometers in length, each contains enough information to make a perfect fit at just one location on the human DNA molecule's twisted, three-billion-rung ladder. So each oligo offers a potential answer to the million-dollar question. It holds the promise of clues that could help prolong lives.

INDUSTRIAL STRENGTH Flatley (left) and Stuelpnagel in the plant where Illumina crafts its cheap, fast DNA analyzers.

PHOTOGRAPH BY MISHA GRAVENOR

HOW TO MAKE A GENE CHIP

Illumina cleverly crams lots of power into its chips. It starts by making a pool of hundreds of thousands of tiny glass beads, each coated with one of some 1,500 types of oligos, DNA fragments that act as sensors (1). When bundles of optical fibers are dipped into the pool (2), a single bead adheres to the end of each fiber (3). Each array includes 96 such bundles (4). A laser scans each fiber to identify the oligo at its tip; the data go onto a CD-ROM (5). When a DNA sample is applied, a laser scans the array again, showing researchers a telltale pattern of reactions (6).



1 Bead pool creation
2 Optical fibers are dipped.
3 Beads adhere to fibers.
4 The completed array
5 Laser mapping
6 The chip at work

FORTUNE GRAPHIC BY JOHN TOMANIO / SOURCE: ILLUMINA

A rival just won approval for a $525 cracker-sized chip that predicts a patient's ability to metabolize antidepressants and other drugs.

For Illumina CEO Jay Flatley, oligos are also the raw materials of riches. They are the key components of Illumina's DNA micro-arrays, commonly known as gene chips. They are mass-produced disposable devices that are fueling the life-sciences revolution much as computer chips fueled infotech. Ranging from paperback-book size down to the size of a bookmark, gene chips offer scientists and drug developers low-cost tools of unprecedented power and sensitivity for unlocking genetic secrets. Hinting at the scale that the business has the potential to attain, Flatley says, "We hope that someday everybody will be genotyped at birth."

The very opposite of a mad scientist, Flatley, 52, is a quiet, silver-haired Chicago native who holds degrees in economics and industrial automation. He loves to show off Illumina's factory—if it can be called that. It's actually more like a lab, with 20,000 square feet of brightly lit rooms populated with Oligators, gene-chip assembly machines, chip scanners, and data-crunching gear. Flatley proudly notes that the plant is small and cheap. "We have the lowest manufacturing cost of anyone in the market," he says. There is only $5 million in capital tied up here, he says, and he points out that the place is fairly deserted. Not many people are needed to run Illumina's production equipment, in part because Illumina ingeniously harnesses self-assembly, a nanotech method, to simplify its chipmaking and drive down costs.

Illumina is one of a half-dozen companies that have sprung up to capitalize on the sequencing of the human genome, which was completed in 2003. They're racing to create technology that will take us from that historic achievement to the age of personalized medicine, in which diagnosis, treatment, and even prevention are tailored to people's genetic peculiarities. That's the dream, anyway. Today personalized medicine is still mostly research—scien-

tists using gene chips to probe the workings of inheritance and its role in health and disease. That's a $1-billion-a-year market, which is growing at a 15% annual rate. A brand-new example of this type of inquiry is the proposed Human Cancer Genome Project, a nine-year, $1.35 billion effort in which researchers at many institutions would compare the genetic sequences of thousands of tumor samples with healthy tissue to identify mutations that cause the disease.

Gene chips also play a major role in drug development and in the nascent field of drug rescue (see preceding story). The benefits of gene-chip analysis are coming within the reach of your family doctor too. Roche Diagnostics recently got FDA approval for its AmpliChip, a $525 device about the size of a cracker that predicts an individual's ability to metabolize prescription drugs for heart disease, depression, and other ills. Medical labs will use it to help doctors zero in on optimal medicines and doses.

Illumina is vying against Affymetrix, the industry pioneer, and other rivals including Agilent Technologies, GE Healthcare, Nanogen, NimbleGen Systems, ParAllele BioScience, and Perlegen Sciences. Affymetrix is the industry leader. The 13-year-old company became profitable in 2003 and last year reported net income of $48 million on revenues of $346 million. Illumina lost $6.2 million on revenues of $51 million last year and expects to become profitable this year.

The pecking order in this fast-moving field is far from set, because no one knows the best way to build a gene chip. Like jousting species in Darwinian evolution, the winners will be companies whose chips deliver the most accurate answers to billions of tiny questions at the lowest cost. And the technology is changing so rapidly that today's leaders could be vaporized by a newcomer with a brilliant innovation.

Illumina was founded in that spirit by John Stuelpnagel, 47, a veterinarian turned biotech venture capitalist, who is now COO. In the late 1990s Stuelpnagel became fascinated by Affymetrix's pioneering efforts at gene chips. Its technique is to painstakingly build up oligos on quartz wafers, one chemical unit at a time, using a photolithographic process like that employed by makers of computer chips. Stuelpnagel smelled opportunity in an alternative method devised by a chemistry professor at Tufts University. In 1998 he licensed the rights and launched Illumina.

A few months later Flatley came to visit the venture. "It was a phenomenal technology," he says. "I fell in love." A veteran gearhead, he was cofounder and CEO of Molecular Dynamics, which built DNA sequencers used in the Human Genome Project and which had recently been bought out (the company is now part of GE Healthcare). "The deal hadn't made me rich enough to stop working," Flatley says, and when Stuelpnagel asked if he would like to run Illumina, he leaped at the chance.

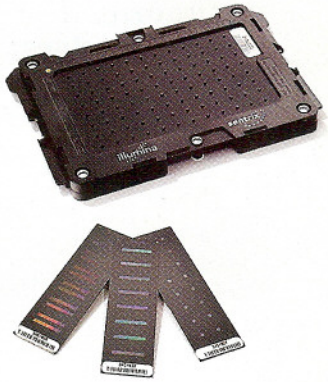
COURTESY OF ILLUMINA (2)

Flatley knew that speed was the name of the game. By 2003, Illumina was making and selling early versions of its chips; even before that, it took advantage of the tech boom to pull off a $100 million IPO. The money gave Illumina the cash it needed to ramp up fast, says Flatley—and to survive the subsequent biotech bust, which wiped out many startups. Illumina's stock, which debuted at $16 a share, fell as low as $1.80; recently it traded at $8.50, and the company still has a war chest of some $50 million.

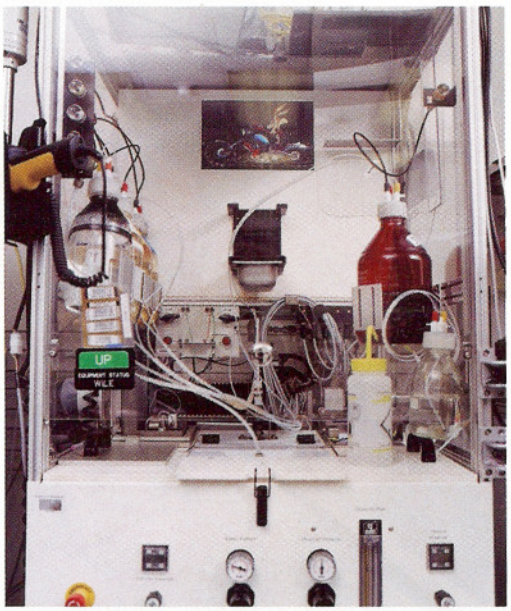
What was the technology Flatley fell in love with? Illumina's clever design begins by attaching hundreds of thousands of oligos, those submicroscopic biological sensors, to glass beads so tiny that several dozen would fit onto the period at the end of this sentence. Under high magnification, the beads look like fuzzy tennis balls. Illumina creates hundreds of batches of beads, each batch bearing a different oligo that will seek and latch onto a specific sequence of a DNA sample.

Next the batches of beads are mixed to form a "pool" into which bundles of microscopic optical fibers are dipped (see illustration, "How to Make a Gene Chip"). Each fiber— there are 50,000 per bundle—has a minute pocket chemically etched into its end; when it touches the bead pool, the fiber picks up a single bead, which nestles firmly in the pocket. Thus treated, the bundles are then assembled into a book-sized array.

It doesn't matter which spot a bead finds; by letting them "self-assemble" on the fibers, Illumina avoids the large cost of trying to accurately position scads of infinitesimal components. Instead, the company uses an ingenious "decoding" process in which a laser scans the bundles after the beads have come to roost, identifying each oligo sitting at the end of a glass fiber. This is like being able to magically iden-



TOUCHED BY A ROBOT An automated dispenser extends needle-like pipettes to place chemicals onto the surface of an array. Bottom: Illumina's Sentrix array and smaller cousins.



MISHA GRAVENOR

CALL ME OLIGATOR
This $100,000 gizmo churns out billions of short DNA segments called oligos that serve as gene chips' submicroscopic sensors.

tify all the people in a vast crowd from a high-flying airplane. The resulting unique map of all the oligos on the chip is stored on a CD-ROM that is shipped to the customer with the chip. By working with such tiny beads, Illumina crams impressive analytical horsepower onto its products: Some 500,000 oligo beads do their detective work simultaneously on the Sentrix Array Matrix, Illumina's flagship product, which is the workhorse in many genomics labs.

Customers put all this to work by dipping the array into a specially treated DNA sample. As the sample wets the beads, each oligo looks for the unique DNA sequence it is built to detect. If the sequence is present, the oligo chemically binds to it and then lights up when a finely focused laser is beamed through the array; if the sequence is absent, the oligo stays dark. The pattern of tiny lights winking on across the array translates into a torrent of information about the sample being tested. Such patterns of light may someday yield definitive answers to those million-dollar questions about individual susceptibility to disease.

Like jousting species in Darwinian evolution, today's gene technology leaders could be driven into extinction by a brilliant newcomer.

Illumina's technology helped it trump rivals in supplying most of the gene chips for a six-nation, $100 million follow-on to the Human Genome Project known as the International HapMap Project (the name derives from blocks of DNA called haplotypes). The project takes aim at giant barriers of expense and practicality that are impeding genetic science. The Human Genome Project created a Mount Everest of knowledge—vast and sublimely beautiful, yet hugely costly to get at and essentially untamed. Even though technology is evolving fast, sequencing an individual's genome is still prohibitively expensive—$10 million, by current estimates. Before doctors can apply genomics routinely to the needs of individuals, scientists must distill genetic knowledge into practical chunks that are affordable to get.

The goal of the HapMap project is to chart some shortcuts. On a genetic level, any two people are approximately 99.9% identical. It's in that remaining 0.1% of the genome that our uniqueness, our susceptibility to disease, and our individual responses to drugs reside. So in recent years scientists have been using Illumina's chips to comb through individuals' DNA samples for telltale variations known as single-nucleotide polymorphisms (SNPs), or "snips." Depending on where in your genome a SNP is located, it can determine whether you have brown eyes or blue, apparently mean nothing at all, or serve as a marker for disease. Illumina's technology has helped bring down the cost of identifying each SNP from more than 50 cents two years ago to just 2 to 3 cents now. The problem, though, is that each person has ten million or so SNPs, making a complete analysis still too costly.

The HapMap project, which in the U.S. is mainly funded by the National Institutes of Health and is due for completion this year, uses an ingenious strategy to cut the cost of genetic analysis still further. Scientists have discovered that most of the human genome is organized into haplotypes. These blocks of DNA pass down pretty much unchanged from generation to generation; locating a few distinctive SNPs can be sufficient to identify an entire haplotype. Thus a few hundred thousand "marker SNPs" can provide a shorthand summary of a person's entire genome, cutting the cost of genetic analysis to a few thousand dollars per person. That's cheap enough for researchers around the world to launch studies comparing, say, the genomes of healthy people with those of people who have a disease. From such studies will emerge fresh ideas about where to aim new drugs. "The HapMap is generating a gold-standard set of variants," says Francis Collins, who shepherded the Human Genome Project to completion and directs the NIH's National Human Genome Research Institute. "If you know that a gene has a variant that predisposes somebody to a disease, that variant becomes the best drug target you can imagine."

Illumina is launching new lines of chips, including one that does "gene-expression profiling." Built to detect which of a person's genes are active or inactive at a given time, the chip generates information thought to be central to fully unraveling the secrets of health and disease. Flatley is also moving the company aggressively into the low end of the market—making DNA technology for drug research and diagnostics. In February he bought CyVera, a Connecticut maker of technology for those applications, for $17.5 million in stock and assumed debt. That will enable Illumina to compete with Affymetrix and other rivals across a broader range of products—and boost its chances of being around decades hence, when gene chips are in everyone's medicine chest. F

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