

Gene Machine

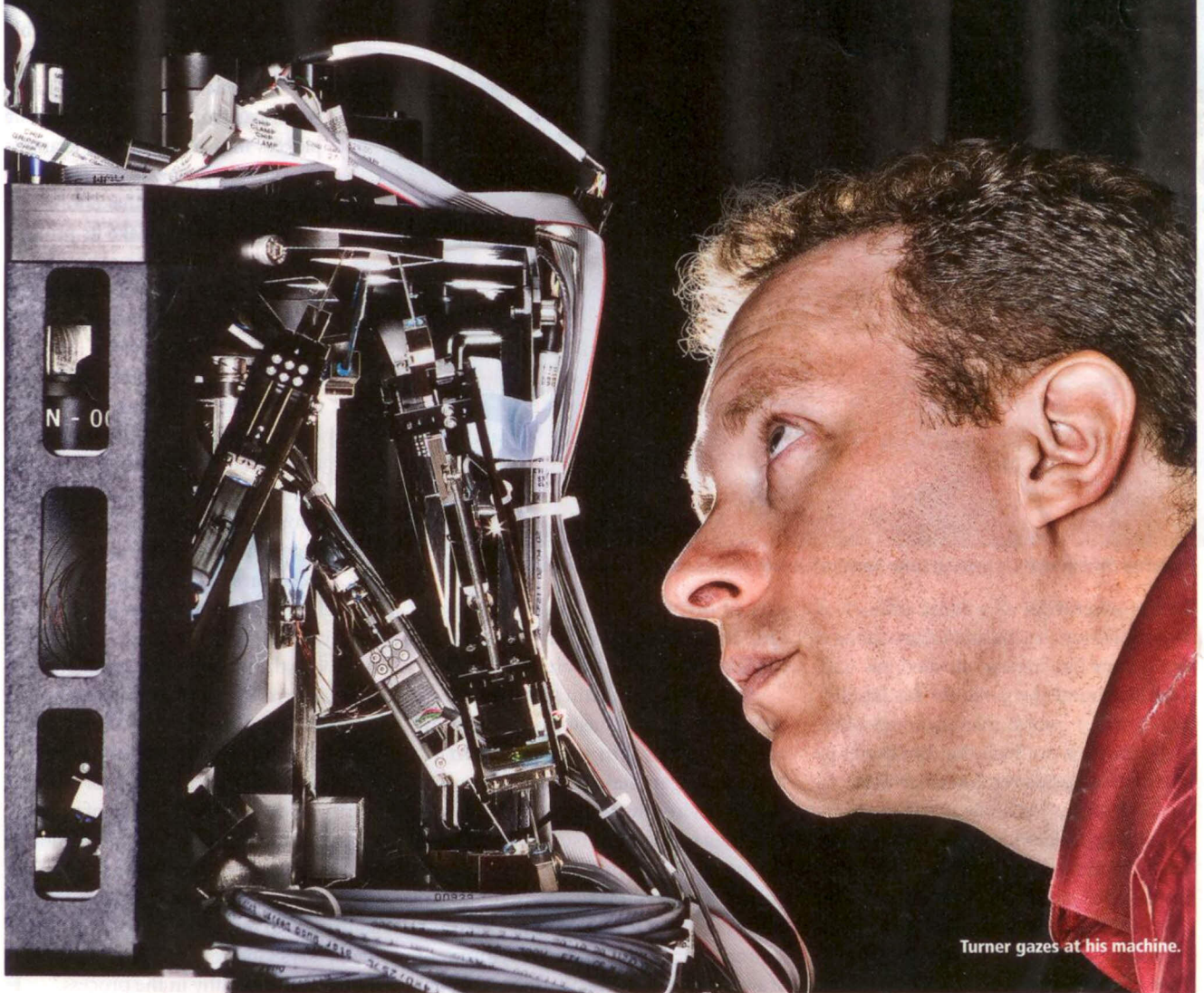
There are lots of companies out there decoding the human genome. Steve Turner's DNA scanner is radically different. By Matthew Herper

ON THE GROUND FLOOR OF AN OFFICE BUILDING in a rundown neighborhood in Menlo Park, Calif., two lasers fire inside a dresser-size aluminum alloy cabinet. The beams bounce off mirrors and through lenses toward a foot-high, six-legged contraption that looks like a robot insect. There they converge in the center of a glass slide the size of a fingernail on a point the diameter of the head of a pin.

That point is full of thousands and thousands of tiny holes,

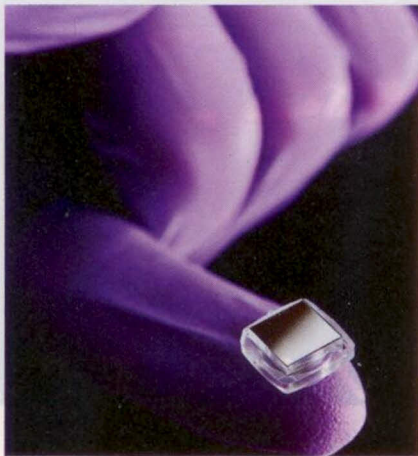
each smaller than the smallest transistor. Roughly a third of the holes contain tiny loops of DNA circling through a mutated enzyme in a soup of molecules tagged with luminescent dyes. Each letter of genetic code creates a tiny flash of a different color of light, which is picked up by a camera and read into a computer.

This is a prototype of the fastest DNA decoder ever built. When finished it should be capable of sequencing millions of DNA letters in 15 minutes, compared with the days or weeks



Turner gazes at his machine.

PHOTOGRAPHS BY ERIC MILLETTE FOR FORBES



The chip on which the DNA is sequenced.

it takes current machines. It is the brainchild of a soft-spoken physicist named Stephen Turner, 41. With a buddy in grad school at Cornell 12 years ago he hatched the idea of sequencing the genetic code in nanotech holes. In 2000 he founded a company to make his idea real. During a venture capital drought for biotech in the early 2000s, he and his wife, another physicist, emptied their savings of \$65,000, more than they made together in a year, to keep the company afloat.

Today Turner's company, Pacific Biosciences, is being compared with Google, Apple and Intel for the disruption it could create in biology and medicine. Using the machines, researchers working on viruses will be able to look at thousands of specimens and get instant results. Plant genomes, unreadable with many of the current machines, will be rendered clearly. Researchers at Stanford have taken the PacBio machines beyond DNA, using them to look at the proteinmaking machinery that is inside every cell. In essence, the PacBio machine could become a powerful molecular microscope that allows researchers to, for instance, watch drugs block enzymes and use that information to build better ones.

"I think everyone agrees that if they succeed, they own the business," says Roger Kornberg, the 2006 Nobel laureate in chemistry and a member of PacBio's board. "The potential of their approach is exceptional."

Right now the genome industry is fixated on the fierce race to execute cheaper and faster DNA sequencing. The cost of sequencing a person has dropped from \$1 bil-

lion in 2000 to \$1 million in 2007. Illumina, a San Diego company that rules the \$6 billion market for genetic chips, this summer started selling human genomes at \$50,000. Complete Genomics in Mountain View, Calif., a new firm that is selling sequencing as a service, is already predicting it can get the per-genome cost as low as \$5,000 next year by doing a lot of genomes at once.

Turner predicts that his machines will in the next few years sequence nine times more DNA at a clip than the first-generation products, thanks to improvements in chemistry. By 2013 a new machine could improve performance another tenfold. "Using a drop in a vial, you'll generate the entire genome," insists Eric Schadt, a former Merck geneticist and now PacBio's chief scientific officer.

PacBio is now building ten test versions for delivery early next year to institutions such as Monsanto and big academic genome centers. It plans to begin selling finished versions in next year's second half. The price has not been revealed but is expected to be in the \$600,000 range (not counting hundreds of thousands of dollars for the chemicals involved). The company, which has 280 employees, has raised \$260 million in venture capital and is hungry for more, as it expects to spend a total of \$350 million before its projected profitability in mid-2012. The next batch of cash may come from the public next year.

The modern age of DNA sequencing began in 1992 when maverick J. Craig Venter recognized that by using lots of existing gene-sequencing machines he could sequence an entire organism, a bacterium. The same expensive process was used by both the govern-

ment-run Human Genome Project (price tag: \$3 billion) and Venter's rival effort at Celera Genomics in Rockville, Md.

At Cornell in the late 1990s a biochemist by the name of Jonas Korlach worked down the hall from his friend Steve Turner. Korlach had another idea to sequence DNA that he thought could be cheaper and as quick.

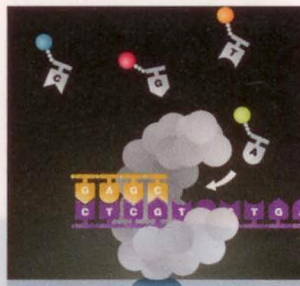
The technology at the time required that DNA be cut up into tiny pieces, transferred into bacteria and then put into machines that figured out the genetic code by sorting, by length, the letters of the genetic code: A, T, G and C, also known as adenine, thymine,

guanine and cytosine. But this process requires huge numbers of DNA molecules and lots of expensive chemicals.

Korlach instead proposed the idea of eavesdropping on how the body copies DNA in its cells. After all, it reads and copies the entire genome every time a cell divides. Capturing this process was the challenge. DNA is a zipperlike molecule, with the A-T-C-G letters as teeth. Because A binds only to T and G binds only to C, unzipping—and re-zipping—it makes two identical copies. It was easy enough to tag the letters with fluorescent dyes. The hard part was detecting the tiny bit of light that the dye would produce. That's where Turner's nanotech came in. What worked best was a sheet of glass, with a thin coat of aluminum with tiny holes drilled into it.

Others in the lab doubted that you could patent a sheet of metal with holes drilled in it, but it gradually became clear that the holes, dubbed zero-mode wave guides, were ideally suited to capturing and

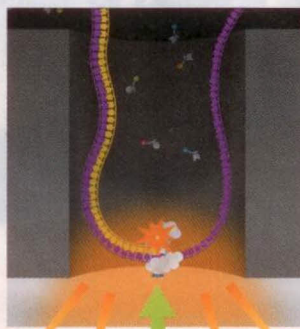
HOW IT WORKS



DNA is copied by an enzyme in PacBio's machine.



The DNA letters used to make the copy have been tagged to emit tiny flashes of colored light.



A camera can catch these tiny flashes thanks to a 50-nanometer hole that screens out other light.

THE DNA DASH

OTHER COMPANIES RACING TO MAKE GENE SEQUENCING FASTER, CHEAPER AND MEDICALLY USEFUL.

LIFE TECHNOLOGIES CARLSBAD, CALIF.

Formed by merger of Invitrogen and sequencing pioneer Applied Biosystems last year.

ILLUMINA SAN DIEGO

Its new, fast machine has made it the company to reckon with in sequencing.

454 LIFE SCIENCES BRANFORD, CONN.

One of the first of the current generation of sequencers; owned by Roche.

COMPLETE GENOMICS MOUNTAIN VIEW, CALIF.

Has used a factory approach—send them DNA, they'll sequence it—to finish 14 human genomes.

OXFORD NANOPORE OXFORD, U.K.

Another nanotech entrant; has a development deal with Illumina.

ION TORRENT GUILFORD, CONN.

New, under-the-radar company from founder of 454.

then reading tiny signals of light.

Turner formed a company, Nanofluidics, but it ran aground for lack of funding. Turner and his wife used their savings to pay for patent applications, so that Cornell would no longer own a share, and for research overhead, so he would qualify for a grant from the National Institutes of Health.

He continued work, and in January 2003 his paper describing the first prototype was featured on the cover of the prestigious publication *Science*.

The work caught the attention of William Ericson, a partner at Mohr Davidow Ventures in Menlo Park, Calif. Most VCs were uninterested in gene sequence—the human genome project was done by then—but Ericson thought someday cheaper sequencers would be needed and invested \$5.5 million (later increased substantially).

Turner quit Cornell in May 2003 and moved out west to found PacBio. He agreed to relinquish the chief executive job to focus on research. Hugh Martin, a former telecom executive, heard about the company and talked his way into the chief executive slot. Korfach, who had helped invent the technology, joined in March 2004.

While the PacBio folks were starting to

build their machine, the genome revolution was advancing. Newer, cheaper machines drove down the cost of sequencing dramatically. In 2007 a company called 454 Life Sciences sequenced the genome of James Watson, the discoverer of DNA's structure, for \$1 million. Complete Genomics recently announced it has already sequenced 14 human genomes for organizations including Pfizer and Harvard University at a cost of \$20,000 each. Instead of selling gene sequencers, Complete is using a factory-style approach, driving down costs by doing lots of genomes at once. It says it will sequence 10,000 human genomes next year. "The big challenge for any new sequencing company is that sequencing is already getting very cheap," says Isaac Ro, a genomics analyst for investment bank Leerink Swann.

Mindful of the competition, PacBio is starting to talk up the way its machines can be used for things competitors can't. Nicholas Schork, a professor at the Scripps Institute in San Diego, is using PacBio technology to try to understand why some drug-resistant bacteria are more deadly than others. Current high-speed DNA sequencers can assemble only tiny stretches of DNA, which must be puzzled together using supercomputers. This can miss cases when changes in the order of otherwise identical DNA turn once mild germs into killers, he says. PacBio looks at bigger puzzle pieces.

PacBio's machine can also sequence material other than DNA, making it potentially a superpowered microscope. Many viruses, for instance, are made of a related chemical called RNA. PacBio can sequence the RNA directly, which competitors can't, potentially allowing researchers to better understand why some flus are worse than others.

PacBio's machine has also allowed Stanford researchers to watch the structure in cells, called a ribosome, which makes proteins from DNA code. A better understanding of the ribosome could lead to new antibiotics, a third of which work by mucking up bacterial ribosomes.

At the moment the prototypes are in pieces on the floor, as engineers fine-tune them to make them more stable. Turner and his colleagues seem to be having fun. The machines are all named after characters from *The Simpsons*. **F**