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How Do You Like Your Genes? Biofabs Take Orders

By ANDREW POLLACK

INDUSTRIAL age foundries made cast-metal parts. Information age foundries, or "fabs," produce computer chips. Now come foundries for the biotechnology age, churning out the stuff of life itself.

Such "biofabs" produce made-to-order genes, the stretches of DNA that contain the instructions for living creatures. The foundries take orders over the Internet from pharmaceutical companies or academic scientists and ship back the finished genes in as little as a week or two. The genes can be used to genetically engineer bacteria or other cells to make proteins, or in various types of biological research.

Sales of the gene-synthesis industry are estimated at only $50 million a year, but they are growing rapidly. One foundry, GeneArt, in Regensburg, Germany, has gone public. It says it expects sales this year to increase at least 60 percent, to 12.5 million euros, or about $17 million.

Fueling the surge is the productivity of DNA synthesis, which has increased 700-fold in the last decade, according to Bio Economic Research Associates, a consulting firm. The cost per base pair, the basic chemical unit of a DNA molecule, has dropped to less than $1, from about $30.

The ability to make genes has given rise to a field called synthetic biology, which might lead to artificial life in a few years. For now, though, most of the biofabs' business is coming from transforming the practice of 30-year-old "conventional" genetic engineering.

"The prices have come down to the point where it is less expensive for many researchers to have a gene synthesized than to make the equivalent molecule themselves," said John Mulligan, chairman and chief scientist at Blue Heron Biotechnology, a gene-synthesis company in Bothell, Wash.

Genetic engineers generally extract a gene from an organism. Then they might modify it or put it in a different organism. The gene for insulin, for instance, can be extracted from human cells and put into bacteria, which will produce insulin for use by diabetics. It is a cut-and-paste operation, like writing a phrase by snipping the necessary words out of magazines and gluing them together in the proper order.

Gene synthesis, by contrast, is like typing the phrase on a word processor. Scientists specify the sequence of the desired gene and have it "printed" at the foundry. They can do this because the complete genome sequences of humans and many other species are available in databases.

Peter Kuhn, an associate professor at the Scripps Research Institute in San Diego, has been studying the proteins made by the virus that causes SARS, which killed nearly 800 people in 2003.

Before the introduction of gene synthesis, Mr. Kuhn had to isolate the genes from the virus itself, then put them into bacteria to have them produce the proteins. Now he orders the genes from DNA2.0, a foundry.

"If we were starting this today, I wouldn't even bother trying to get any of this from the natural source,"

Mr. Kuhn said. “I would just order everything.”

DNA is made up of four chemical units called bases, usually represented by the letters A, C, G and T. The bases are paired to form the rungs of the twisted ladder structure of DNA.

The first mail-order DNA companies sprung up about two decades ago, selling short, single-stranded pieces of DNA, usually 20 bases to 60 bases long. These strands, called oligonucleotides, or oligos, are used to help find and amplify full genes.

Sales of DNA oligos are about $700 million a year, according to BioInformatics, a market research firm, though some executives say that figure is too high. Production is automated and competition is cutthroat, with prices of 10 cents to 50 cents a base.

Customers “want to have it delivered to them the next day and they really don’t want to pay much for this custom service,” said Mary Buchanan, a business manager at Invitrogen, a leading supplier of oligos. Other major participants include Integrated DNA Technologies and Operon Biotechnologies.

The newer biofabs make complete double-stranded genes, usually hundreds to about 2,000 base pairs long, though in a few cases, longer than 10,000. Leaders in this business include GeneArt, Blue Heron, DNA2.0, which is in Menlo Park, Calif., and Codon Devices of Cambridge, Mass.

Customers usually place orders — a sequence of hundreds of As, Cs, Gs and Ts — through a biofab’s Web site or by e-mail. “It’s really not possible to take an order like that over the phone or even by fax,” said Jeremy Minshull, president of DNA2.0.

Manufacturing is a prime example of what is called mass customization, highly automated production with every single product being different.

The machines that string together bases make so many mistakes that they cannot make a full gene flawlessly. So the companies make shorter oligos and splice them together. Error checking is crucial.

A new opportunity for foundries could come from synthetic biology, which involves designing cells almost from scratch to perform specific tasks, like producing biofuel. Synthetic biologists envision writing the DNA code for such cells the way computer programmers write software. Then the DNA would be manufactured and put into cells.

Ultimately, it might be possible to create artificial life. The scientist J. Craig Venter is trying to do that by synthesizing the 580,076-base genome of a simple bacterium, which would be inserted into some other bacterium.

Some biofabs are distancing themselves from such talk, fearing it could arouse public distrust. “We are not in the business at Codon of creating life,” said John P. Danner, president of Codon Devices.

There is concern that DNA synthesis might be used to make pathogens. In 2002, scientists at Stony Brook University announced that they had synthesized the polio virus, using its published genome sequence and mail-order oligos. It took them three years, but a sequence that long, 7,500 bases, can now be made in weeks.

The foundries say they screen orders against a database of pathogen DNA sequences and verify that

customers are from reputable institutions. The leading companies have formed a consortium to write other safeguards and regulations.

But critics say governments should devise the regulations. ETC Group, a technology watchdog, said that regulations were needed to prevent ill-advised or careless applications, not just nefarious ones.

“The danger is not just bioterror,” ETC said in a report earlier this year, “but ‘bioerror.’ ”