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Double Helix With a Twist; Do Fewer Genes Translate Into Fewer Dollars?

By ANDREW POLLACK

Incyte Genomics advertises access to 120,000 human genes, including 60,000 not available from any other source. Human Genome Sciences says it has identified 100,000 human genes, and DoubleTwist 65,000 to 105,000. Affymetrix sells DNA analysis chips containing 60,000 genes.

But now it turns out there might be only around 30,000 genes. If that's the case, what exactly have these companies been selling?

The new gene tally -- 26,000 to 40,000 -- is among the most significant findings in rival papers by Celera Genomics and the public Human Genome Project, which competed to determine the entire sequence of the human genome. For science and the genomics business, the papers are landmarks. But they could also contain some land mines.

In particular, the consensus of the two rivals that humans have far fewer genes than anticipated could raise questions about the credibility of the genomics approaches used until now. It could also mean that developing drugs based on gene studies will be quicker than anticipated -- but also present a smaller business opportunity.

Moreover, if a human might have only a third more genes than a roundworm, which has 19,000, that indicates that genes alone cannot explain human biology. So companies and investors will gravitate toward the next big buzzword, proteomics, the study of the proteins.

The lower number of genes also suggests that gene hunters have already received or applied for patents on a greater proportion of total genes than anticipated -- leaving less room for newcomers. But if genes are not the whole story, it also means those patents could be worth less.

At the very least, the lower gene count will be used by Celera to sling mud at competitors like Incyte and Human Genome Sciences. That could help Celera sell its main product, a database of gene information it provides to drug companies for millions of dollars a year.

"They're going to have some real explaining to do," gloated J. Craig Venter, Celera's president, who said other companies had inflated their gene numbers to make their technology look more valuable. The full genome sequence, he said, will be "a truth serum for the field."

The competitors defend their approaches and dismiss Dr. Venter's charges as a transparent marketing ploy. "They have to say something about a worthless database," huffed William A. Haseltine, chief executive of Human Genome Sciences, which, like Celera, is based in Rockville, Md.

Indeed, some of the scientific papers appearing in the journals Nature and Science this week appear to contain some truth serum for Celera as well. They assert that Celera's gene sequence is not noticeably better than the free public sequence, although Celera disputes these analyses as too simplistic.

Even without any truth serum, however, the genomics business has already been given a dose of humbling reality. Stocks soared last year on hopes that the completion of the human DNA sequence, announced at the White House in June, would revolutionize the pharmaceutical business. And dozens of young companies with techniques for finding or analyzing genes went public on a wing and a prayer.

But many genomics stocks have come down to earth as investors have come to realize that having the "book of life" is just one step on a long road to developing drugs.

In fact, a new study by Lehman Brothers and McKinsey & Company concludes that genomics could actually double the pharmaceutical industry's research and development costs per drug, at least over the next few years. New genes and proteins are being discovered so rapidly, the report says, that drug companies are being overwhelmed with potential paths to pursue. But since the roles of these genes and proteins in the body are not well understood, there is a greater chance that drugs will fail after costly clinical trials, the report says.

Investors are also having doubts about companies that sell tools, information or services to drug companies, rather than develop drugs themselves. Last year, the tools approach was considered a quicker way to profitability, avoiding the long clinical trials, huge investments and risk of failure inherent in drug development.

But sentiment has shifted. Now drugs are seen as offering the biggest potential payoff. They can be sold for years, while gene analysis techniques can become obsolete quickly. And, some analysts say, there is too much competition in tools. There are at least 10 technologies, for instance, for detecting genetic variations among people.

So virtually every genomics company is now tripping over itself to become a drug company.

The stock of Celera, which is primarily an information provider (though it, too, is moving into drug development) is down 83 percent from its peak a year ago. Incyte, another database provider, is down about as far. But Human Genome Sciences, which already has drugs in clinical trials, is down only about 54 percent. Last year, genomics stocks in general fell 9 percent, while the entire life sciences sector rose 24 percent, according to indexes maintained by Burrill & Company, a San Francisco investment firm.

The papers published this week in Nature and Science will focus attention again on genomics and could rekindle investor enthusiasm, lifting stocks. Celera shares rose $6.15, to $47.75, yesterday and other genomics company shares also rose, although less impressively. But the impact could be small.

"Investors last year were enamored by the science," said Winton G. Gibbons, an analyst at William Blair & Company. "Now what we need is the movement to medical discoveries, not scientific discoveries."

Still, there could be long-term implications. Mr. Gibbons said having fewer genes was good news. "We get to drugs and profits faster than if we have to sort through 100,000 genes," he said.

But others say it means more limited prospects for genomics companies and less of a cornucopia for drug companies.

Jean-Michel Claverie, who heads a genetic information laboratory run jointly by the French government and the drug manufacturer Aventis, argues that only 10 percent of genes can be expected to provide good targets for drugs. So if there are only 30,000 genes, that means 3,000 targets, a number the drug industry could work its way through in a few years.

"One can seriously question the long-term sustainable growth and economic viability of the whole industry," he writes in a commentary in Science this week. "The 'end of the beginning' of the genomic era might thus be followed by the 'beginning of the end' very quickly."

But other experts dismiss this argument. First, they say, even 3,000 targets would be a huge increase. All the drugs that exist today are aimed at a total of only 500 different protein targets in the body. Moreover, the new genome papers show that the complexity of the human body results not so much from having more genes than simpler creatures, but from having many more proteins.

Genes, which are segments of DNA, are of interest to drug companies primarily because they are the recipes for making proteins. But it is the proteins that actually carry out bodily functions, and drugs are developed to bind to particular proteins.

It was once thought that knowing the gene would be enough to know the protein. But in humans, more so than in simpler creatures, this is turning out not to be the case. Genes are made of pieces that can be spliced together in different combinations. So one gene can make more than one protein.

Genomics alone, therefore, cannot answer everything drug companies need to know. This is giving new impetus to the emerging field of proteomics, which seeks to identify all proteins and how they relate to one another. But proteomics is far more daunting than genomics, because proteins are more complex than genes and also more plentiful, probably numbering in the hundreds of thousands.

Celera is plowing full bore into proteomics, but other companies have head starts. Just last month, Large Scale Biology, based in Vacaville, Calif., said it had compiled a database of more than 115,000 human proteins. Hybrigenics, a French company, published a map showing about half the interactions of the proteins in the bacterium linked to ulcers and stomach cancer. And the Cytogen Corporation of Princeton, N.J., said it had mapped the interactions of one of the roughly 70 families of human proteins.

The fact that one gene can make more than one protein also partly explains the wide variation in estimates of gene numbers.

Celera and the Human Genome Project independently estimated the number of genes by taking the entire genome -- about three billion letters -- and performing various computer analyses to try to determine which small parts of that sequence contain the code for proteins. DoubleTwist, based in Oakland, Calif., also did a computer analysis yielding a much higher figure, a sign that such computer models are subject to wide variations.

Incyte and Human Genome Sciences find genes by catching them in the act of making proteins. They search human cells for the messages sent by the genes to the cell's protein-making machinery.

But since one gene can make different proteins, and therefore send out different messages, the assumption that each message comes from a different gene leads to an overcount. Also the technique actually detects not whole messages but fragments of them. So different fragments of the same message might be incorrectly assumed to represent different messages.

Incyte, which advertises that it has 120,000 genes, now says what it really means is 120,000 messages, which would translate into 40,000 genes if each gene is assumed to make three proteins. Roy A. Whitfield, chief executive of the Palo Alto, Calif., company, said the message information was more valuable than genes anyway because it is more indicative of what proteins are being made.

But Dr. Haseltine of Human Genome Sciences insists his company has found 100,000 genes, not messages. He said the computer methods used by Celera are so primitive they simply missed more than half the genes. "Genome sequencing is probably the worst way I know to find genes," he said.

As if confirming that, AlphaGene, a genomics company in Woburn, Mass., said recently that it used the message technique to find 264 genes on chromosomes 21 and 22 -- the first chromosomes fully sequenced -- that had been missed by the Human Genome Project scientists.

Affymetrix, the leading manufacturer of DNA chips, has always made clear that its chips contain 60,000 genes or messages. Such chips are used to measure which genes are active, or "expressed" in a cell. Measuring which genes are turned on in a tumor cell but not a healthy cell, for instance, could provide clues to the causes of cancer.

Stephen P. A. Fodor, the chief executive, said Affymetrix would now begin producing chips using the completed genome sequence. Such chips will provide far more information than chips made using the messages. Rosetta Inpharmatics of Kirkland, Wash., describes the usefulness of a similar technique in a paper in Nature this week.

But to Dr. Venter of Celera this just confirms his contention that the information produced until now is of limited value. "The whole gene expression field," he said, "is going to start over from scratch."

Correction: February 14, 2001, Wednesday

An article in Business Day yesterday about the business implications of the first analysis of the human genome compared the number of genes in humans and roundworms incorrectly. Humans have about 50 percent more genes, not just one-third more.

Organizations mentioned in this article:
Celera Genomics; Incyte Genomics; Human Genome Sciences Inc

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