Where the future went

In response to market trends and patenting laws, genomics companies are adapting their strategies

In July this year, Celera Genomics (Rockville, MD, USA) placed its formerly proprietary genome sequence data into the public domain, thereby ending the first grand business experiment in the era of commercial genome sequencing. In 1998, Celera vowed to use its shotgun-sequencing method to outrace the publicly funded Human Genome Project and complete its own draft sequence. Sparked partly by fears that Celera could obtain commercial control of the human genome, the public project boosted its efforts and finances to match the challenge.

When both drafts of the human genome sequence were published in February 2001, Celera's version was widely considered to be superior to the public sequence, which was immediately released for general use. Celera set out to profit from its effort by licensing its database—and subsequent databases of mouse and rat genome information—to companies and academic institutions. It was an initial success, but the customer base eventually dwindled. Celera and its parent company, Applera Corporation (Norwalk, CT, USA), saw the writing on the wall, and split the business into separate diagnostics (Celera Diagnostics) and drug discovery (Celera Genomics) companies in 2002. The move to make its data public is a gesture of goodwill from Celera, but it also stands to benefit its sister company, Applied Biosystems (Foster City, CA, USA), which supplies researchers with gene-expression assays and other research tools.

Throughout its history, Celera has been a bellwether. Many companies, such as Incyte (Wilmington, DE, USA) and CuraGen (New Haven, CT, USA), joined the genome market in the late 1990s. The Incyte expressed sequence tag (EST) database, which contained DNA from normal and diseased tissue, was also a highly valued resource for biomedical research and drug development. However, like Celera, Incyte saw demand drop as the publicly available National Center for Biotechnology Information GenBank database increased in quality. Similarly, Incyte transformed itself into a drug discovery and development company.

The experiences of Incyte and Celera illustrate the changing value of genetic data. Adaptations to patent laws and the increasing quality of publicly available databanks have caused raw data—and the genetic targets gleaned from them—to decline in commercial value. As a result, companies that initially concentrated on acquiring and selling genetic data are now moving into other more promising research areas.

During the heady days of genomics, there were two broad categories of genomics companies. Some, like Celera, generated sequence data or single-nucleotide polymorphism (SNP) data and licensed access to the information. Others mined available data sources—public or private—in the hopes of finding genes involved in disease-relevant biological pathways. Both business models faltered. Similar to the data generators, data miners saw a steady decrease in the demand for their insights. "There are only so many large pharmaceutical companies that you can sell this information to. It's not a bottomless pit of opportunity," commented Mario Ehlers, chief medical officer at Pacific Biometrics, Inc. (Seattle, WA, USA).

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The downturn that began in 2000 led to a buyer's market in early-stage technologies and information, which then caused venture capitalists to attempt to acquire late-stage opportunities at early-stage prices, said Ehlers. "It almost killed the investment opportunities in these very early-stage discovery and genomic activities. All the emphasis is on who has a product in the clinic, and how many years they are away from approval and demonstrated revenues. All the excitement about

the untold riches that would be mined [from the genome], that's pretty much over now. [Companies are saying to themselves], 'we've got to focus on a few plausible targets, on our drug candidates or diagnostic products, and develop them to a stage of significant value where we can partner with a bigger company.'"

Most scientists agree that Celera's data lost commercial value as the public sequence information caught up in quantity and quality. The Incyte database also lost its lustre. "We weren't getting any new information out of it anymore," said Scott Presnell, director of scientific computing at ZymoGenetics (Seattle, WA, USA). In fact, the company no longer relies on proprietary ESTs for target identification but uses predictive algorithms of its own. ESTs are used only for confirmation, "and for that, publicly available ESTs are sufficient," Presnell said.

Another important factor in the declining value of genetic data sets has been changes in patent law. During 2004, the US, European and Japanese patent offices became significantly more restrictive in their requirements for patenting DNA and protein sequences. "Whereas before I could have a rather broad claim to a large genus of protein or gene sequences, now they're restricting me to things that I pretty much have in hand," said John Kilyk Jr, managing partner at the law firm Leydig, Voit and Mayer (Chicago, IL, USA). The agencies have also overhauled their fee structures. In the past, companies would pad their patent applications with extra claims that might be useful in the future. Now, the US Patent Office charges US\$200 for every claim beyond the first three. Applications that once cost US\$1,000 or US\$1,500 to file now routinely cost up to US\$10,000, according to Kilyk.

Together, those changes make it more difficult for companies to shield large proprietary databases. Instead, Celera is placing its database in the public domain, hoping to reap good public relations and perhaps indirect financial rewards. "To

protect a database would be prohibitively expensive, unless you know for sure that you have a winner in there. That has to weigh in the thinking of these companies. The patents are narrower, and that means they're also tougher to enforce," Kilyk commented. These changes might also reflect a backlash against the freewheeling patent applications of the past. "There was a definite sense that in the biotech field things had gotten carried away. There were a few years there where it seemed like you could get anything you wanted if you spent enough time and effort," Kilyk said.

As a result, genomics companies are adapting their strategies. Some are transforming themselves into drug discovery companies, using their genetic data internally to discover and exploit gene and protein targets. Others continue to provide access to the data, but with further restrictions. These companies might allow others to mine their data at will, with the provision that, if it leads to a commercially useful discovery, the database owner receives compensation. "I tell my clients all the time, patents are just one tool. You don't have to have a patent to have a license agreement or to make money from something at a later time," Kilyk pointed out. "You can sit on this giant database and file 100,000 patents. You'll have spent a ton of money on [intellectual property] lawyers and filing fees, and in 20 years they expire anyway." Instead, companies can make their data available to everyone, in the hope that someone else will use the information to find a therapeutic or diagnostic product. "You might as well get people started, especially given how long it takes to get [the end product] approved [by the US Food and Drug Administration]," said Kilyk.

Despite the market saturation and stricter patent requirements, genetic information retains a high value. Most pharmaceutical companies concentrate on their later-stage products; however, eventually, they will have to restock the pipeline, which will increase interest in basic sequence data. "I think the market value [of genetic and protein targets] went down, but their inherent value remains very high," said Glenn Schulman, manager of marketing and investor relations at CuraGen, which has also seen a transition from genomics to drug discovery. "I think it will come full circle and these early targets will become more valuable." Genetic data

will also become more important for clinical trials, as pharmaceutical and biotechnology companies are moving towards personalized medicine, in which patients might be prescribed specific drugs based on their genetic makeup.

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When it comes to identifying targets, the true value of a data set is determined by the extra non-genetic information it contains. Well-annotated, well-characterized and retrospective sample sets are therefore particularly valuable, according to Rowan Chapman, director of life science research at Mohr Davidow Ventures (Menlo Park, CA USA). She cites Genomic Health (Redwood City, CA, USA)—a company in which Mohr Davidow holds a stake—which has access to a database of genomic information from women with breast cancer with known outcomes. With genes and expression patterns at hand, Genomic Health does not have to conduct prospective clinical trials to establish their relevance. "Before, we were cataloguing, now we're subsetting the universe [of genes] and assigning relevance," said Chapman.

Similarly, the Utah Population Database (UPDB) is a collection of genealogical information and medical records that reference more than 11 million people. The UPDB does not contain genetic information *per se*, but the familial relationships can be invaluable to companies searching

for genetic targets, as 60–70% of the database members are related in some way to the founding families of Utah, according to Stephen Prescott, professor of internal medicine at the University of Utah, and founder and chief executive officer of LineaGen (Salt Lake City, UT, USA), a non-profit organization that aims to enhance the research efficacy of the UPDB. If an individual has a rare mutation associated with a disease, or a genetic profile that predicts the outcome of cancer, it is easy to find even distant relations that might provide more clues.

LineaGen has several agreements, including one with Celera, for access to the UPDB for use in genetic studies and clinical trials. Prescott views the databases of Celera and Incyte as valuable resources that eventually ran their course. "It was a self-limited model," he said. Incyte, for example, obtained tissues from various sources and profiled their gene expression. "But once the target was discovered or the project [terminated], there was no value in going back to that data set. You couldn't go back to the individual [for further study]." The UPDB allows exactly that. Prescott envisions development programmes in which companies use the database to identify a target, develop a drug and then return to members of the database to recruit individuals for clinical trials. That sort of iterative study is not possible with stagnant databases.

LineaGen is not the only company with access to valuable population databases. deCODE Genetics (Reykjavik, Iceland) works with the Iceland database of medical records and tissue samples, which includes information on most Icelanders since the end of the Second World War. The

genetically isolated population also has well-established genealogical records that date back to the first Scandinavians who settled on the island in the ninth century.

Even if Celera's original business model of selling access to sequence data has turned out to be unviable, it has nevertheless benefited research as a whole. The Human Genome Project started without any private sector impetus, but the public effort was largely accelerated in response to Celera, owing to fears that a private company could end up controlling the intellectual property rights to the human genome. This race to the finish resulted in the Project being completed earlier than expected, and gave scientists worldwide an enormously valuable research tool. In addition, the public data have been continuously improved and updated, to almost match the quality of Celera's proprietary data.

Will a public-private competition, similar to that which drove the Human Genome Project, happen again? It is already occurring, many say, but with less fanfare and in the opposite direction. In the 1990s, the efforts of the publicly funded project prompted Celera to join the fray. Today, public initiatives are staking a claim on industry's turf. Chapman believes that the work of Celera and Perlegen Sciences (Mountain View, CA, USA) in the area of genetic haplotypes—adjacent SNPs that are typically inherited together—prompted the establishment of the International HapMap Project in 2002. This seeks to catalogue haplotypes for use in identifying genes that are important in disease, and in individual responses to pharmaceutical drugs and the environment. Perhaps in response to commercial efforts, the National Cancer Institute developed the Cancer Genome Anatomy Project to compile gene expression profiles on normal, precancerous and cancerous cells.

Celera's legacy also extends beyond genetics. In 2004, the National Institutes of Health (Bethesda, MD, USA) established the PubChem chemical database. The project is, at least in part, intended to

counter industry's increasing monopoly on chemical compounds. "It's like a public version of the big compound libraries that big pharmaceutical companies have in-house," said Ehlers. The project provides information on the biological activity of small molecules, along with their chemical structures, and allows researchers free access to carry out computerized screening, structure modelling and drug design.

So, how will history view Celera and its challenge to the public sequencing project? It is too early to judge it as a success

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or failure, as the story is not yet finished. "They did the right thing by their shareholders," Chapman said, before pausing. "Strike that: they did the right thing by a subset of their shareholders. Should they have gotten out earlier? I don't know. But they pushed science forward."

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The squeaky wheel gets the grease

Research funding is not necessarily allocated to those who need it most

A recent television advertisement in the USA featured a woman in her 30s remarking that, since she was a teenager, she had feared getting breast cancer. After all, one in seven women is now diagnosed with the disease, up from one in nine when she was younger. After years of regular breast self-examinations and mammograms, she was diagnosed with cancer—lung cancer, despite being a non-smoker. The voice-over at the end of the advertisement commented that nearly twice as many women now die from lung cancer each year than from breast cancer.

How the issue—and fear—of breast cancer came to occupy such a prominent place in the consciousness of women worldwide, while lung cancer stealthily became the new killer, illustrates the power of public relations campaigns and patient activism. Together, these forces have brought numerous diseases, including breast cancer, prostate cancer and HIV/AIDS, to the attention of millions. They have raised record amounts of private funding for research and are putting considerable public pressure on the government to adjust its biomedical research agenda. As philanthropic funding is limited, various patient groups fiercely vie for

the public's attention and contributions—and ultimately government funding. The public is increasingly confronted with 'duelling' statistics—which disease is worse, has higher mortality and is harder to treat—that compete for their attention and dollars. There is no parallel campaign, however, to raise money to develop new drugs for tuberculosis, even though one-third of the human race is infected, and 1.75 million died of the disease in 2003.

The Prostate Cancer Foundation (PCF; Santa Monica, CA, USA) is one such activist group, which has mounted an aggressive awareness campaign to draw attention to their cause. Junk-bond millionaire and prostate cancer patient Michael Milken founded PCF in 1993 to fund applied research, and the foundation now boasts an advisory board with former US presidents and numerous captains of industry. Its website and public relations material issue dire warnings that "without improvements in diagnosis and treatment, by 2015 the number of new [prostate cancer] cases will increase 50% from about 230,000 today to over 300,000...A non-smoking man is more likely to get prostate cancer than lung, bronchus, colon, rectal, bladder, lymphoma, melanoma, oral and

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