Human Genome Project Spins Off Array of Novel Methods and Technologies

By Mary Jean Pramik

Medical therapeutic miracles remain the primary promise of the Human Genome Project (HGP) (see p.1). But pharmaceutical R&D does not occur in a vacuum. Several new technologies, including novel developments in DNA sequencing and mapping methods and the optimization of instrumentation, are rapidly spinning off genome-related companies. Many genome scientists are now involved in taking a new discovery and turning it into a financial venture. The new technology firms cover a wide "product" area with each company attempting to find its marketing niche in a rapidly evolving industry.

BIOS Laboratories (New Britain CT) , for example, has the reputation of being "just a reagent company" to some. According to Richard Kouri, Ph.D., BIOS president, the company has expanded its research efforts to optimize uses of DNA and RNA products.

"We have just won a $500,000 SBIR grant to develop a series of kits for coupled amplification sequencing," Dr. Kouri tells *GEN*. The CAS method allows researchers to perform direct genomic sequencing in one step, he says.

BIOS is also exploring possible liaisons with instrumentation suppliers such as Pharmacia (Piscataway, NJ) and the Applied Biosystems division (ABI, Foster City, CA) of Perkin-Elmer to determine if the CAS technology can add to the power of tomorrow's automatic DNA sequencers. Kouri estimates a ten-fold cost reduction in sequence determination if BIOS finds the right cycle sequencing instrumentation alliance. BIOS also offers core facility services for small companies that need bulk DNA or RNA isolations and characterizations.

In the area of instrumentation, ABI's work-horse Catalyst™ DNA sequencer has dramatically increased the genome sequencing efforts, particularly by reducing the errors in manual manipulation. The system's data-finder computer chip, licensed several years ago from TRW, not only allows the rapid comparison of acquired data by the individual laboratory but can link up with various DNA libraries throughout the world.

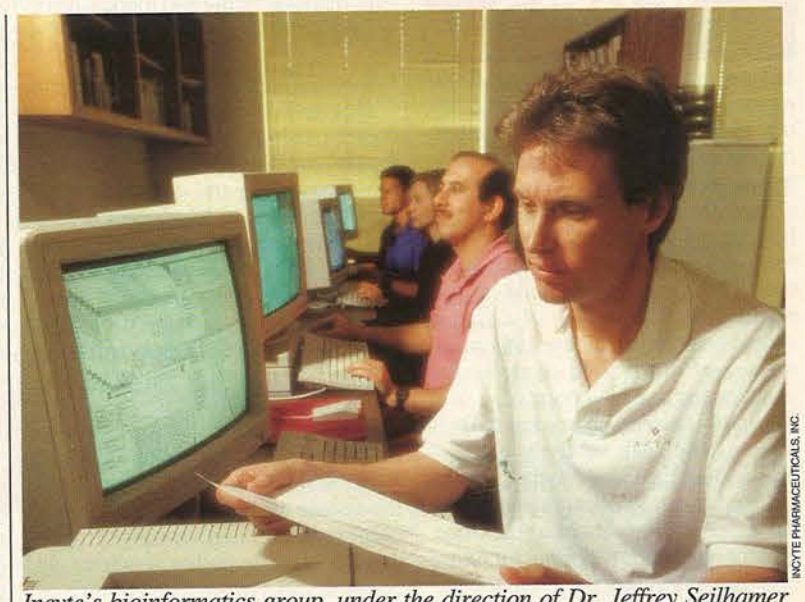
"We are always looking at new technologies since it may be easier for ABI to commercialize them. We continue to have a strong commitment to improve all three areas [sample preparation, separation and data analysis] of the DNA sequencer and allied technologies," says Elaine Heron, Ph.D., a senior scientist at ABI.

"Technology development usually lags behind the biological research areas," notes Maynard Olson, Ph.D., professor of molecular biotechnology at the University of Washington, Seattle. "The general molecular biology methods for cloning DNA and sequencing have advanced rapidly but we have seen no corresponding advance in the automation of these procedures and in instrument development."

Dr. Olson works with Leroy Hood, M.D., Ph.D., Roger Bumgarner, Ph.D., and others in Dr. Hood's newly formed molecular biotechnology department. According to Dr. Hood, his group has a built a prototype machine that can perform DNA sequencing on much smaller samples at a faster pace, approximately 350 base pairs in 1.5 hours. By tweaking lasers, detection systems, gel formulations and other components, Dr. Hood intends to speed up the DNA sequencing process by five- to 50-fold.

"Our primary goal is to develop biotechnology methods and put them into actual practice. If they work, we will look for commercial partners," says Dr. Olson.

Dr. Hood's group has not joined Darwin Molecular Corp. in Kirkland, a genome-based therapeutics start-up, but Dr. Hood does sit on the company's scientific advisory board.

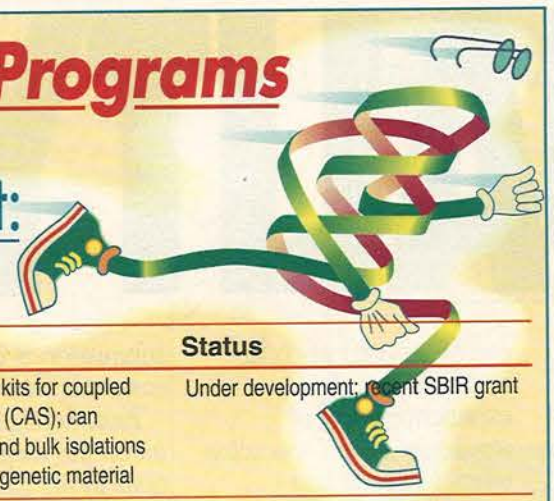


INCYTE PHARMACEUTICALS, INC.

Incyte's bioinformatics group, under the direction of Dr. Jeffrey Seilhamer (front), performs homology and transcript abundance analysis on genes in Incyte's sequence databank identified via high-throughput sequencing of cDNA libraries specific to certain disease states. Using a relational database developed by company researchers, this analysis provides a high-resolution image of tissue and cell-specific gene expression and serves to elucidate the potential pharmaceutical utility of new biotherapeutics and therapeutic targets.

New Startups & Programs

Related to the Human Genome Project:



Sequencing-Related Technologies

Company	Product Area	Status
BIOS New Haven, CT 800/678-9487	Biologicals: DNAs/RNAs kits for coupled amplification sequencing (CAS); can perform as core facility and bulk isolations and characterizations of genetic material	Under development; recent SBIR grant
Collaborative Research Inc. Waltham, MA 617/487-7960	Gene sequencing and mapping based on expertise in high-throughput multiplex gene sequencing; continues to develop, optimize and automate this method	Use their proprietary methods to develop therapies for mycobacterium tuberculosis, manic depression, cancer and others; just signed collaboration agreement with Abbott Laboratories
Genome Systems Inc. St. Louis, MO 800/248-7609	Gene library screening; core facility	Using YAG and P1 phage methods to produce a library; sells sequences
Incyte Pharmaceuticals Inc. Palo Alto, CA 415/855-0555	cDNA sequencing; developed technology that screens thousands of genes/week — called "database discovery"	Plans to focus on pharmaceuticals development using this technology
Millennium, Inc. Cambridge, MA 617/374-9480	Genetic mapping; genomic mismatch screening (GMS)	Developing GMS method licensed from Stanford but intends to focus on therapeutics for obesity, kidney disease and immunological disorders
SEQ Ltd. Princeton, NJ 609/924-3131	DNA sequencing; single molecule sequencing (SMS) by fluorescence	A "virtual company" with two full-time employees, SEQ sells genetic information services to speed up gene discovery
The Institute for Genomic Research (TIGR) Gaithersburg, MD 301/869-9056	cDNA sequencing; using expressed sequence tag (EST) methodology pioneered by Craig Venter to speed up genome sequencing	Goal: to determine which genes expressed by every tissue throughout development and evolution
Instrumentation		
Applied Biosystems Foster City, CA 415/570-6667	DNA sequencer(s)	Developing next generation of sequencers; improve system operations; looking to commercialize new technologies
Genomyx Inc. South San Francisco, CA 415/266-2984	Long read-length sequencers, formatted as a manual, autoradiography-based, medium-priced instrument	Funded by Genentech, instrument system reads 850-900 base pairs at present
Nanotronics La Jolla, CA 619/454-8833	High-speed sequencers	"No public comment" for six months
Research Group		
Department of Molecular Biotechnology, University of Washington, Seattle	Genomic DNA sequencing	Leroy Hood, Maynard Olson and others

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While not direct competition for ABI's DNA sequencers, Genomyx (S. San Francisco, CA) is beta testing its long-read DNA sequencer at their Genentech development site. Genomyx began four years ago with start-up funding from Genentech (S. San Francisco), which holds a significant minority position in the instrumentation company.

A manual integrated unit, the Genomyx sequencer combines proprietary temperature-control technology and configurations, autoradiography methods and reassembly software that can sequence over 1,000 base pairs rapidly, says Frank Ruderman, the company's vp of business development.

"This instrument will revolutionize the way DNA sequencing is done today," he adds. "It will cut off days of reaction time and elapsed time in the DNA sequencing process and thus speed up the method by two to three times."

The company intends to have a model ready for marketing in the next 6-12 months.

Selling Genetic Information

Another market niche carved out by recent genome-related start-ups is providing quick access to gene sequences and gene library information. Who will buy this ready-made information? Both small and large pharmaceutical companies who want a jump on a particular therapeutic market or who do not have an entire gene mapping or sequence department in full operation.

"We basically bring the Human Genome Project to the rest of the world. Our mission is to give scientists access to the information collected by the project," says David Smoller, Ph.D., president of the St. Louis, MO-based Genome Systems. Smoller has used his experience gained as a researcher with the HGP at the Washington University School of Medicine in St. Louis to build a gene sequencing company and library.

Operating through a core facility with access to worldwide gene banks, Genome Systems incorporated in February 1992 and now "sells" pieces of DNA made to order from a customer-submitted DNA probe. If the customer already has the gene, Genome Systems can find the protein. Or vice versa, the company can send in the protein and learn the cDNA sequence in about five days.

Another added advantage of made-to-order genes and proteins is the reduction in cost. Genome Systems charges about $900 per gene sequencing order, much less than the $100/day paid to a technician over the month it takes for this person to sequence the gene. Other expenses such as reagents, instrumentation, insurance, laboratory space, etc. greatly add to the cost of gene discovery and manufacture.

"We anticipate that companies like Merck, Bristol Myers and Genentech will not have to continue to spend millions of dollars on gene discovery in the traditional wet lab with the old cloning techniques," agrees Richard Horan, who heads SEQ Ltd. in Princeton, NJ. The company offers genetic information services, overseen by chief scientist Kevin Ulmer, Ph.D. SEQ Ltd. is developing a proprietary technology known as single molecule sequencing (SMS) by fluorescence to reduce both the speed and cost of DNA sequencing by "several orders of magnitude." According to Horan, the company's new methods will make retrieving genetic information about 2,000 times cheaper than today's cost of $1-5 per base pair.

"It's a bit like crossing the ocean in a row boat or an airplane. Either way, you do cross the ocean," said Horan.

The In-Betweens

Several new DNA sequencing companies also have one foot in the door of the pharmaceutical industry. They have decided to position themselves as drug discovery facilities with their DNA sequencing expertise and technologies promoting product development. Occupants of this niche include Incyte Pharmaceuticals Inc. (Palo Alto, CA), Collaborative Research, Inc. (Waltham, MA), and Millennium, Inc. (Cambridge, MA).

After 30 years of operation, Collaborative Research Inc. (CRI) has divested itself of its genetic and cancer diagnostic testing business and reagent division to focus chiefly on genome-based drug discovery. Using gene mapping, DNA sequencing and bioinformatics methods, CRI is now developing and optimizing its computer-assisted multiplex sequencing technology to increase gene throughput by ten-fold over the next two years. The company intends to continue its contract research efforts for the Federal Government (NIH, NIMH, NCI) and for various foundations such as the Muscular Dystrophy Association while forming drug development partnerships in areas of mycobacterium tuberculosis, schizophrenia, cancer and other infectious diseases.

Millennium, Inc., intends to use novel gene mapping methods to identify disease-causing genes for the purpose of drug development. The company recently signed an exclusive licensing agreement with Stanford University to develop the genomic mismatch screening (GMS) method to accelerate the mapping of multigenic traits.

Millennium's main goal is to develop targeted therapeutics for disorders with genetic components like obesity, kidney disease and immunological diseases.