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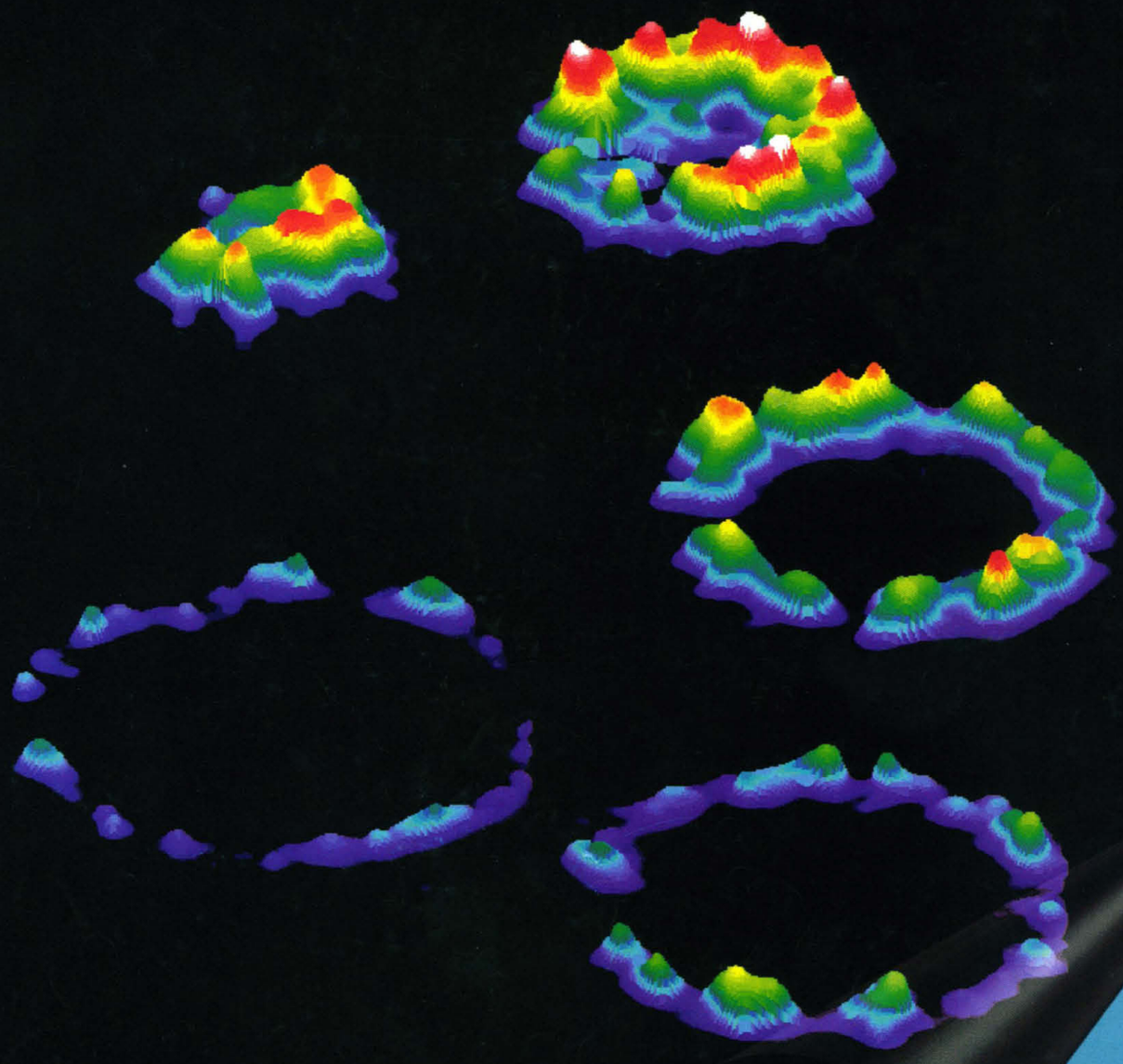

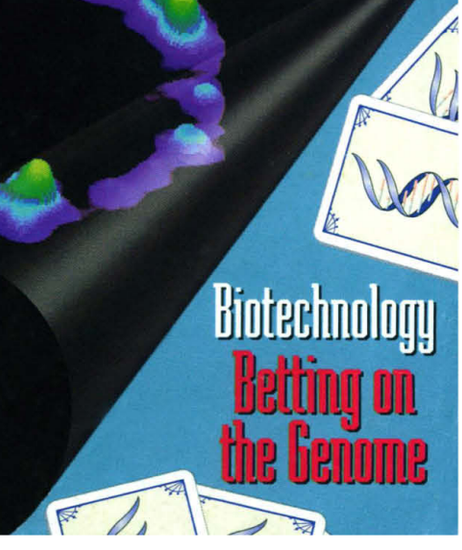

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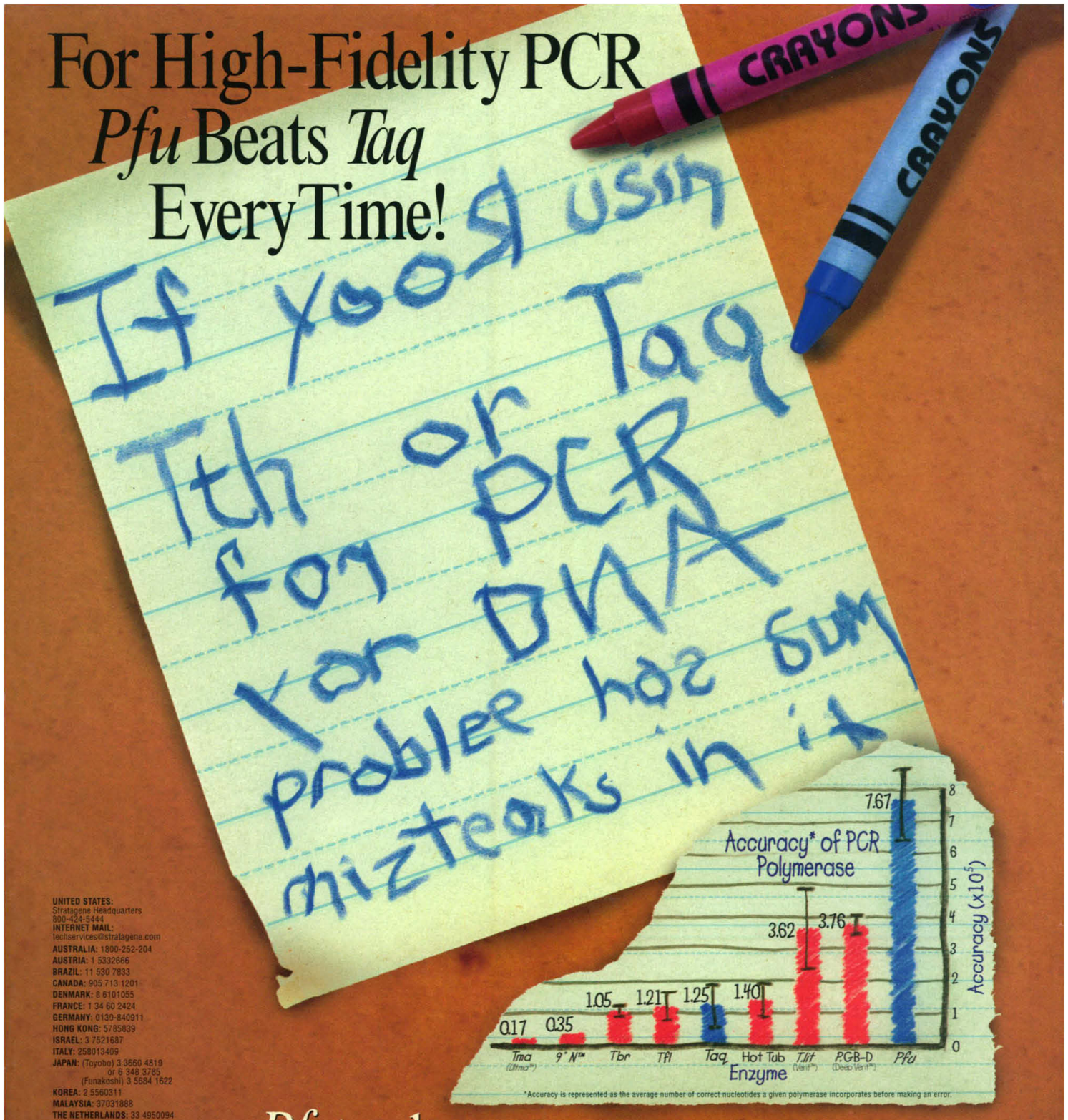

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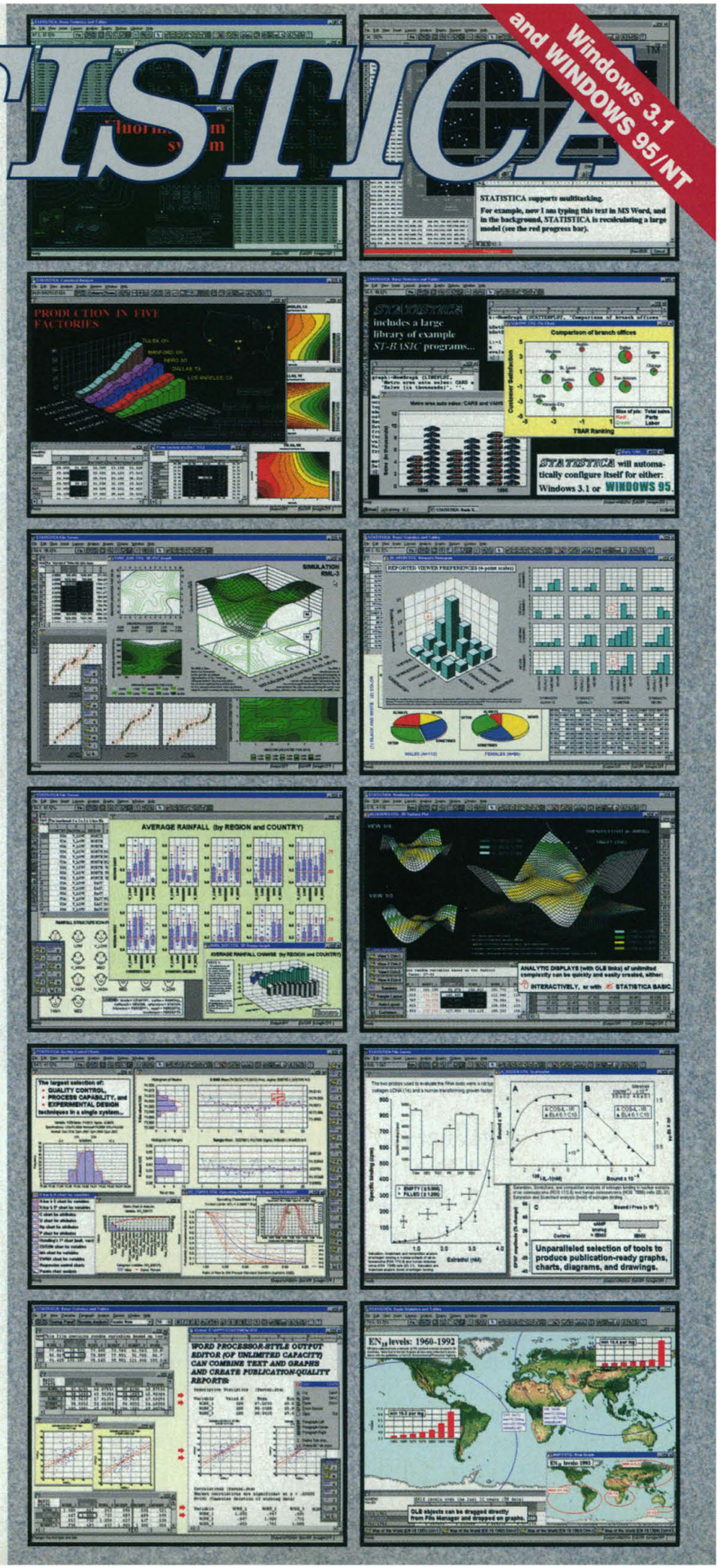

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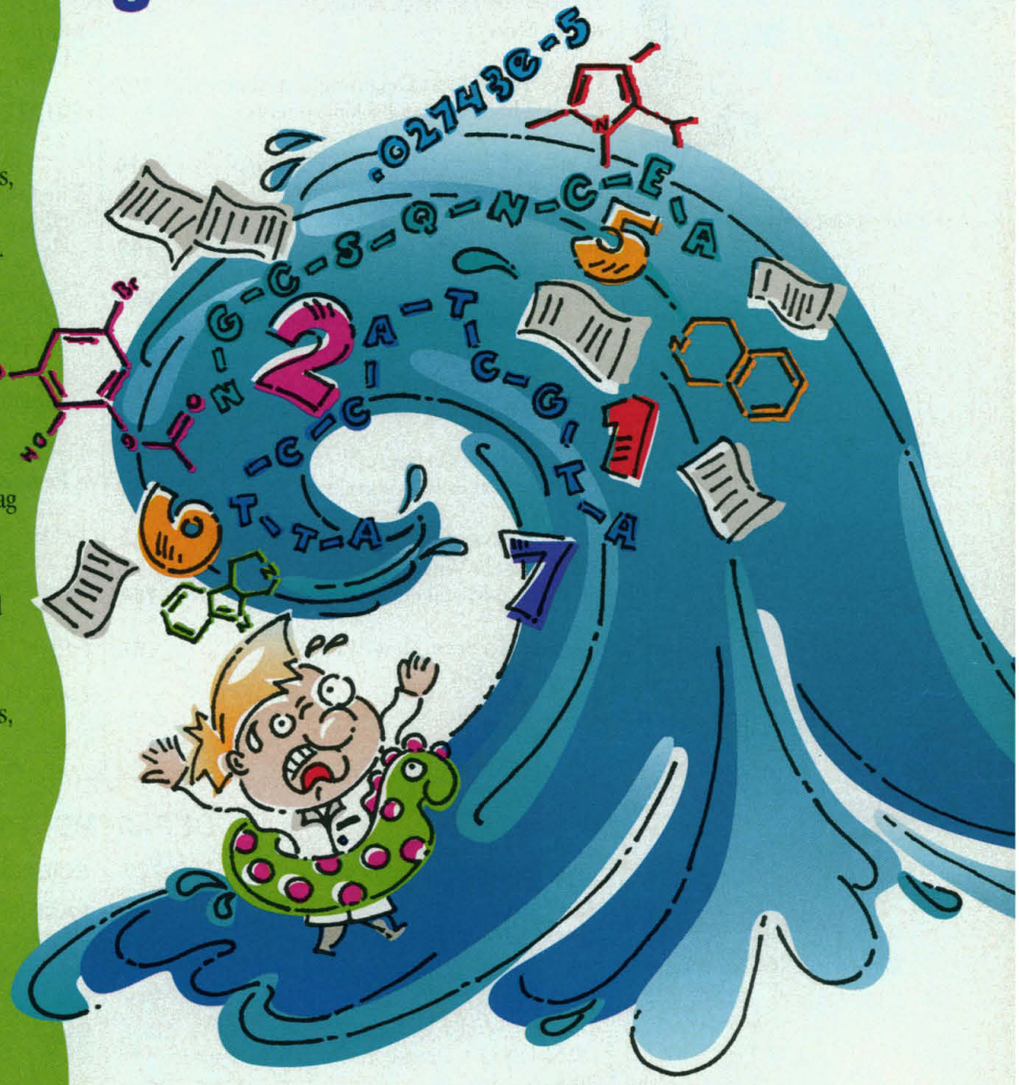

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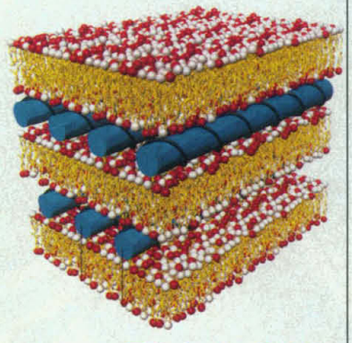
Flowing hot and cold



791 & 810
Ordered DNA-liposome structures

NEWS & COMMENT

RESEARCH NEWS

BIOTECHNOLOGY

BETTING ON THE GENOME

DEPARTMENTS

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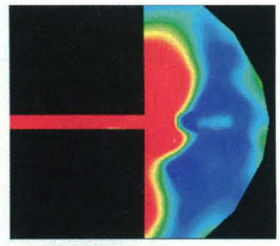
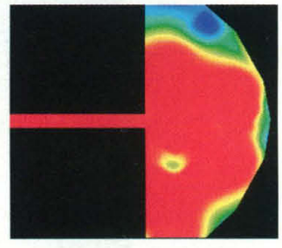
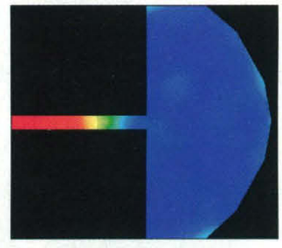
COVER

Propagation of an intercellular calcium wave through glial cells on the surface of the retina. Five frames (clockwise, starting at upper left, 0.93-second intervals) show the leading edge of the calcium wave as it travels outward from the point of stimulation. The wave was imaged by labeling rat retinal astrocytes and Müller cells with a calcium indicator dye and is shown as a pseudocolor image. The largest ring is 190 micrometers in diameter. See page 844 and films at http://enlil.med.umn.edu/www/phsl/work/caw.htm. [Image: E. A. Newman and K. R. Zahs]







841
The beat generation

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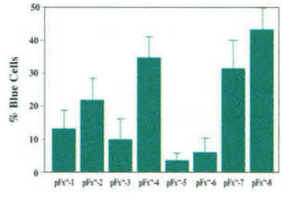

Figure 1: Percent blue cells produced by transfection of CHO cells with a lacZ control vector using PerFect Lipids™ (pFx™1 - pFx™8).

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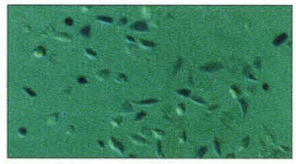

Figure 2: Transfected CHO cells expressing β-galactosidase, stained with X-gal.

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edited by PHIL SZUROMI

Distant relatives

Fossil evidence indicates that primates arose by the Eocene, about 55 million years ago. Although some new finds have provided key information on their early history, some other aspects are uncertain or controversial, such as the relation (and in some cases identification) of early anthropoids (distant ancestors of humans) to other primates. In an article, Kay *et al.* (p. 797) overview recent fossil finds and present a phylogenetic synthesis.

Warming trend

The El Niño–Southern Oscillation phenomenon in the tropical Pacific has a periodicity of 3 to 4 years, but longer term oscillations may be superimposed on these fluctuations. Gu and Philander (p. 805) present a mechanism for these longer oscillations in a model that links the extra-tropics and tropics. Influx of warm water from higher latitudes into the tropics triggers a feedback cycle with an interdecadal periodicity. Such a mechanism may be responsible for the recent but yet unexplained warm conditions that have persisted over the tropical Pacific.

Westward flow

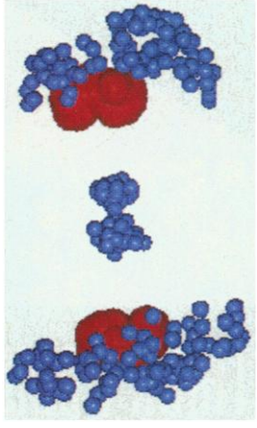
A circumglobal equatorial seaway, the Tethys Seaway, existed during the Cretaceous from about 145 to 65 million years ago, and perhaps even longer ago. It has been suggested that a westward flowing current through this seaway was important in dispersal of fauna and in controlling at least equatorial climates, but numerical models of ocean circulation have had difficulty in reproducing this flow pattern. Bush (p. 807) now reports results from a coupled atmosphere-ocean model in which a westward circumglobal current appears as a robust feature.

Joining the resistance

Hybridization between the sugar beet and related species has brought resistance to pathogenic soil nematodes into the naturally unprotected sugar beet. Cai *et al.* (p. 832; see the news story by Moffat, p. 757) mapped chromosomal breakage points to identify and clone the gene conferring resistance. The *Hs1*$^{pro\text{-}1}$ gene encodes a protein with similarities to those that confer gene-for-gene response to bacterial pathogens.

Clusters within water

Two reports focus on the chemical and physical properties of water and their dependence on cluster size and charge. Gregory *et al.* (p. 814) combined theory and experiment to study the dipole moments of water clusters consisting of two to six molecules. The polarizability of the water hexamer is close to that of liquid water and ice, indicating that the water hexamer may represent the dominant interactions present in these condensed phases. Tuckerman *et al.* (p. 817) present ab initio calculations for the charged water complexes $H_5O_2^+$ and $H_3O_2^-$, which are prototypes of strong and intermediate-strength hydrogen-bonded systems. The quantum character of the shared proton depended on the oxygen-oxygen distance and thus, bond strength; the strong $H_5O_2^+$ complex behaved classically, whereas the $H_3O_2^-$ complex showed quantum effects even at room temperature. These results may also have implications for proton transfer dynamics.



Tagged for ready recovery

A synthetic route is successful only if the desired product can be recovered cleanly. Studer *et al.* (p. 823) have taken advantage of the unusual solubility of fluorocarbon groups to recover products without chromatographic separations. For example, by tagging one of the reactants with a fluorocarbon group, the product, which carries the tag, can be recovered in a fluorocarbon liquid phase. Leftover reactants and by-products will separate into organic or aqueous phases.

Recharging volcanoes

Isotopic studies have provided important information on processes in magma chambers, such as the extent that magmas melt and then mix with adjacent rocks or the amount of mixing with other magmas. Davidson and Tepley (p. 826) show that a detailed record of such processes can be extracted by looking at strontium isotopic variations in zoned plagioclase crystals forming from the magmas. In three case studies, sudden jumps in the isotopic composition corresponded to changes in mineral chemistry and likely mark discrete recharge events.

Visual searching

How do we find the ten of diamonds in a deck of cards thrown faceup on a table? The biased competition model of visual attention suggests that we bias our search for cards with red pips (a top-down factor) and we detect which of these cards most strongly matches the requirements of ten pips and diamond shapes. Rees *et al.* (p. 835) provide evidence from functional imaging studies suggesting that the dorsolateral prefrontal cortex in humans contributes the bias signal to the inferior temporal cortex that mediates object recognition.

Neuron protection

The loss of dopaminergic neurons in a critical spot in the brain, the substantia nigra, is a hallmark of Parkinson's disease. Choi-Lundberg *et al.* (p. 838) have used an adenoviral vector to deliver a neuronal growth factor to just that region of the brain. Tests of this procedure in a rat model of Parkinson's disease show that loss of the neurons after induced degeneration is slowed relative to the rate in untreated rats.

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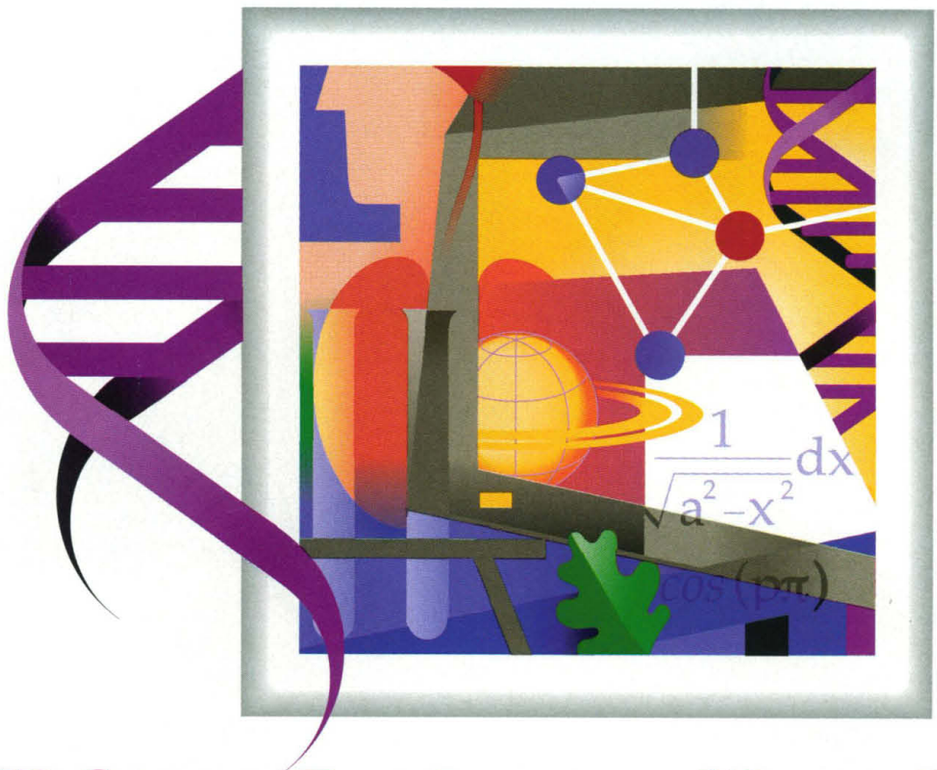

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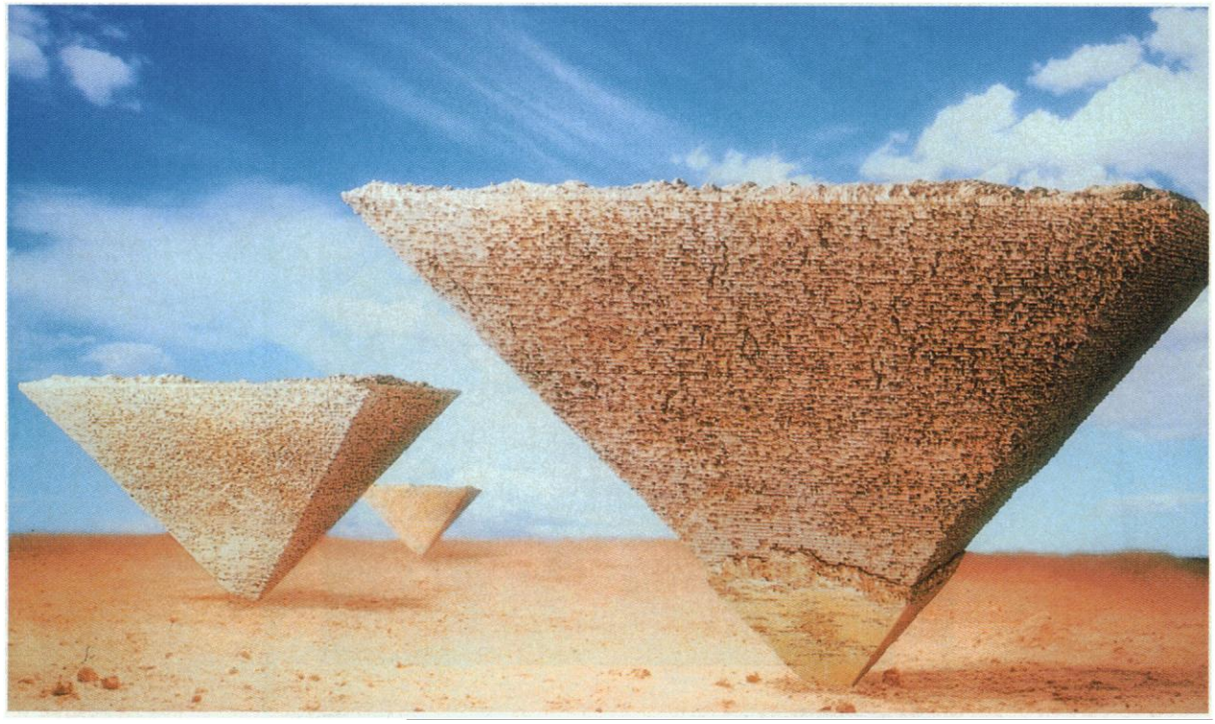

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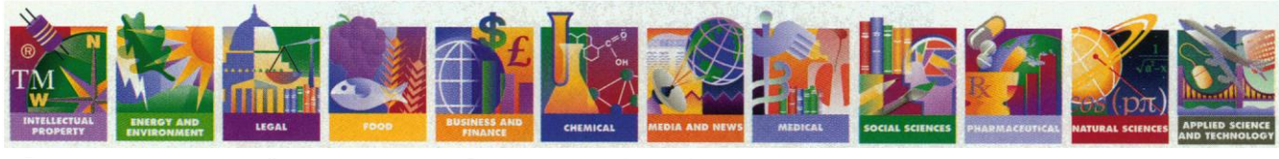

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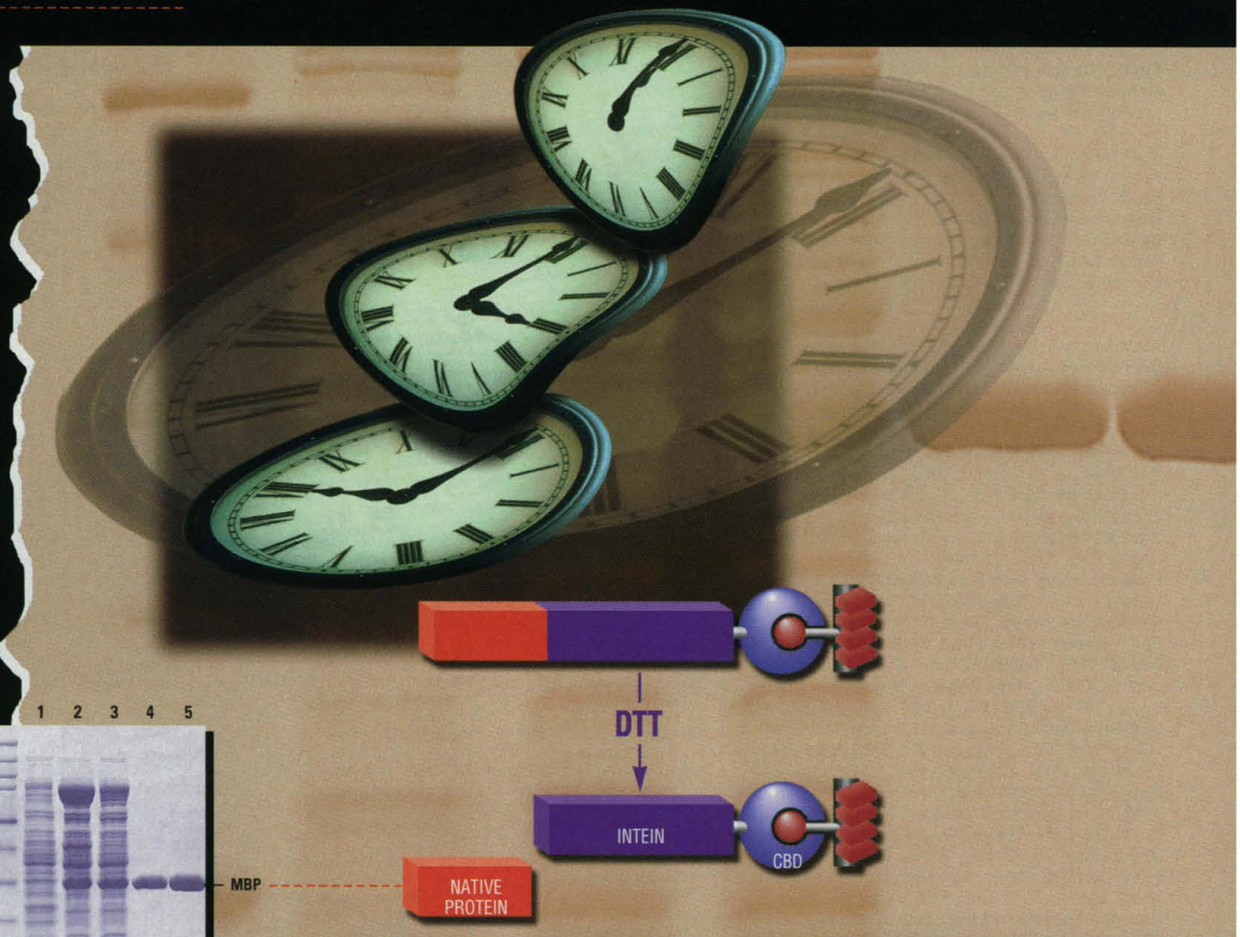

Purification of Maltose-Binding Protein (MBP) with >98% Purity in one step.
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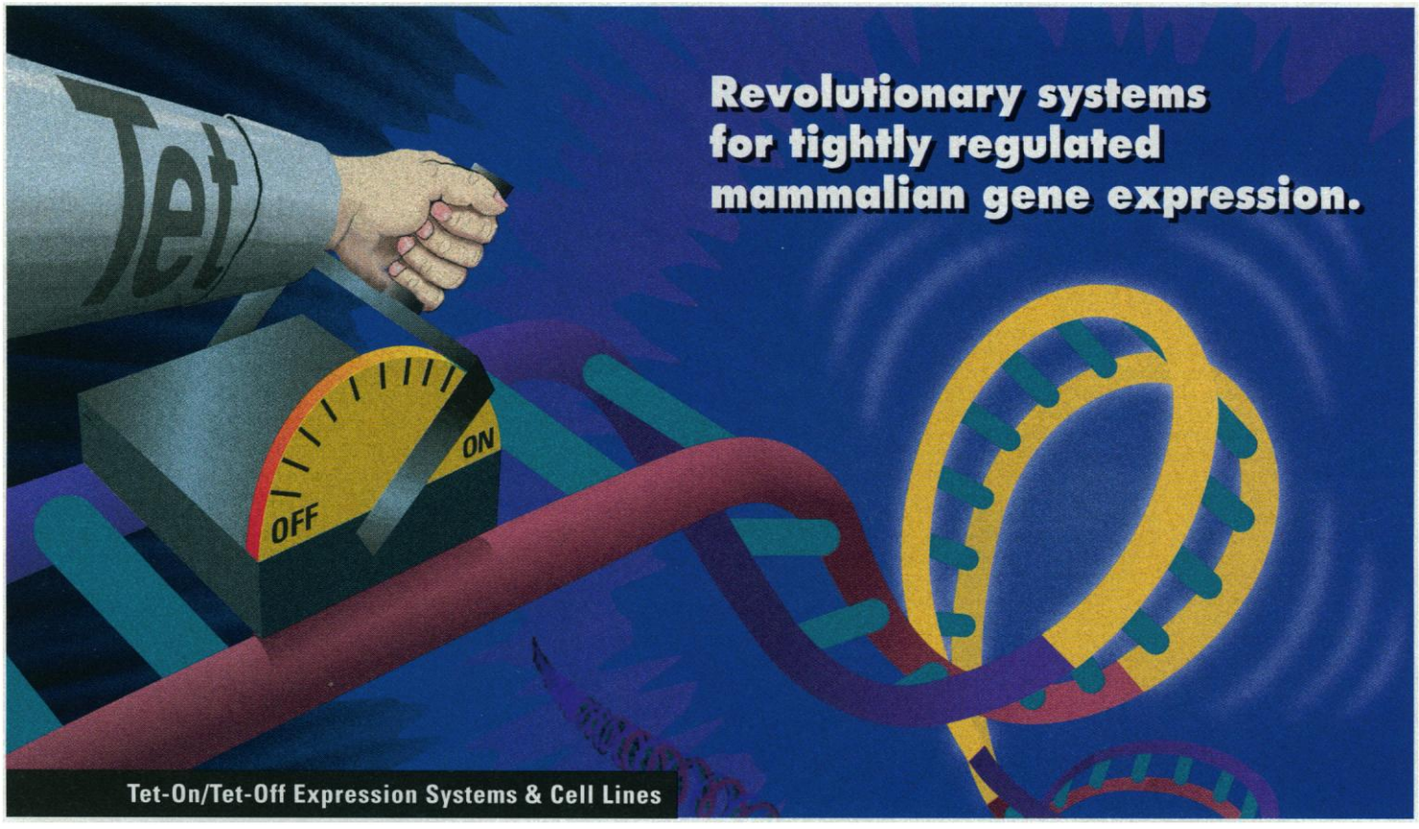

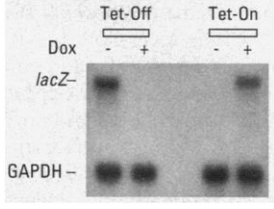

Figure 1. Inducible on/off control of gene expression. HeLa Tet-Off and Tet-On cell lines stably expressing a tet-regulated pTRE-derived plasmid with the *E. coli lacZ* gene were cultured in the absence or presence of 1 µg/ml Dox. For Northern analysis, 10 µg of total RNA per lane was hybridized simultaneously with *lacZ* and GAPDH probes.

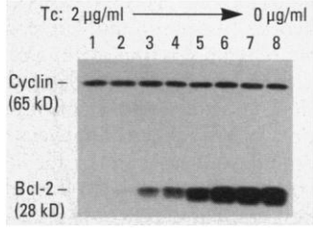

Figure 2. Inducible, high-level expression of the Bcl-2 apoptosis gene. HeLa S3 Tet-Off Cells stably transformed with tet-regulated pTRE-Bcl-2 were grown in 2.0, 0.006, 0.004, 0.002, 0.001, 0.0005, 0.00025, and 0 µg/ml of Tc (Lanes 1–8, respectively). A Western blot containing 100 µg of total protein from each condition was simultaneously probed with human Bcl-2-specific and human cyclin-B1-specific mouse monoclonal antibodies. Tc gave 100-fold induction of Bcl-2.

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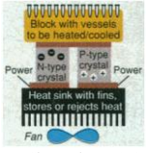
THE MJ RESEARCH NOTEBOOK

Volume VII...No. 1 *A Bulletin of Technological Advance in Molecular Biology* *Winter 1997*

The Peltier-effect Thermal Cycler That Began A Technological Trend: The MJ RESEARCH PTC-100

Left to right: A PTC-100-96AgV with a speedy silver-gold block that can ramp at up to 2.5°C/sec, a PTC-100HB with improved Hot Bonnet heated lid that applies heat and pressure to the tops of tubes or plates for oil-free reactions, and a PTC-100-16MS that holds 16 slides & 24x0.2ml tubes for *in situ*.

How Peltier-effect Heat Pumps Actually Work



The Peltier effect is a solid-state physical phenomenon that was first described by Jean Peltier in the *Annales de chimie* in 1834. Peltier observed that when current passes through a bimetallic junction, one side gets hot and the other gets cold. In the 20th century, this "effect" has been combined with semiconductor technology to construct small, bi-directional heat pumps that are electronic in nature. These pumps are extremely precise and reliable, and they are the basis of MJ cyclers.

RIGHT WAY TO USE PELTIER

It is now widely accepted that Peltier heat pumps are the best technology for thermal cyclers—but exactly how these pumps are applied is critical. A design was pioneered with the PTC-100 where the pumps are mounted between a low-mass sample block and a large, efficient heat sink. Permanent mounting allows fast, efficient heat flow between the pumps and the block. The heat sink can store heat to be later pumped back into the sample block, or it can disperse the heat to outside air—this depends upon the action of a computer-controlled fan.

The Cycler That Went To War in the Persian Gulf and Battled Plague in India

When adversity flared in the Persian Gulf six years ago, the tools of molecular biology were brought to the front. Biological weapons were threatening; means to detect their use were needed. PTC-100s were there—and they did their duty.

In 1994, unsettling reports were circulating that plague had erupted in Surat, India. Indian authorities were addressing the problem as best they could, but the skills to detect *Y. pestis* had atrophied over time. Working with the WHO, MJ RESEARCH donated several PTC-100s, allowing Indian scientists to use molecular methods to battle the disease. In the final analysis, *only* these molecular tests* proved that the plague pathogen was ever present (see *Nature Med* 1:1237-9).

MJ Engineer Paul Titcomb in 1990, with a PTC-100 that was camouflaged by the U.S. Marine Corps for field use in *Operation Desert Storm*.

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* PCR is covered by patents owned by Hoffmann-La Roche, Inc. & F. Hoffmann-La Roche Ltd. Users should obtain license to perform the reaction.

A MUCH-COPIED DESIGN

First Introduced in 1988 and Improved Over Time—It Still Outperforms Most Cyclers

WATERTOWN, Mass.—In 1986 and 1987, much "buzz" was circulating in the biology community about a new method for identifying and amplifying sequences of DNA that was being developed by the Cetus Corporation. A tantalizing paper describing an early form of PCR* had appeared in *Science* in late '85, but a critical refinement—the use of thermostable polymerase enzyme—was not described officially until '88. At that time, the need for significant numbers of instruments to thermally cycle tiny aliquots of biological reagent first became apparent.

The partner of the Cetus Corporation, The Perkin-Elmer Corporation, concentrated on the development of a thermal cycler based upon mechanical vapor compression technology. MJ RESEARCH, INC.—then a year-old start-up company—recognized the opportunity and began development of instrument based upon the more promising Peltier-effect heat pump. Several other companies in the U.S. and England also began development of thermal cyclers—mostly based upon resistive heating and passive air or water cooling (though one other US firm also developed a variant of the Peltier cycler).

In late '88, MJ RESEARCH introduced the world's first Peltier thermal cycler—the PTC-100. Since that time, the instrument's design has been modified, crafted, tweaked—and perfected. To this day, the PTC-100 outperforms most competing cyclers in uniformity, speed, accuracy, and capacity—even though at least twenty other manufacturers have since entered the market. MJ has introduced newer designs—the Mini-Cycler, DNA Engine, and Tetrad—yet the PTC-100 remains a respected workhorse of science.

But perhaps the greatest compliment to this pioneering design is the ubiquitous imitation. Though it was scorned at first by some, the PTC-100's configuration is now mimicked by virtually every manufacturer in every new introduction.

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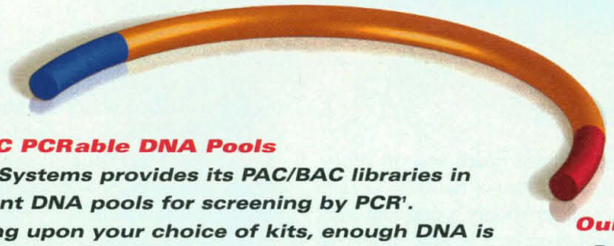

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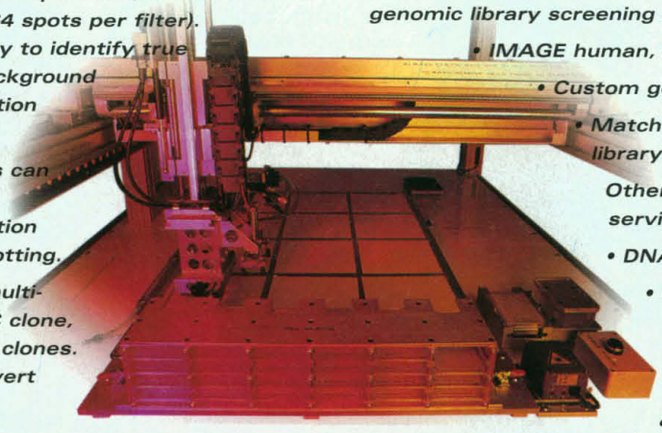

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1. The PCR process is covered by patents owned by Hoffman-La Roche.

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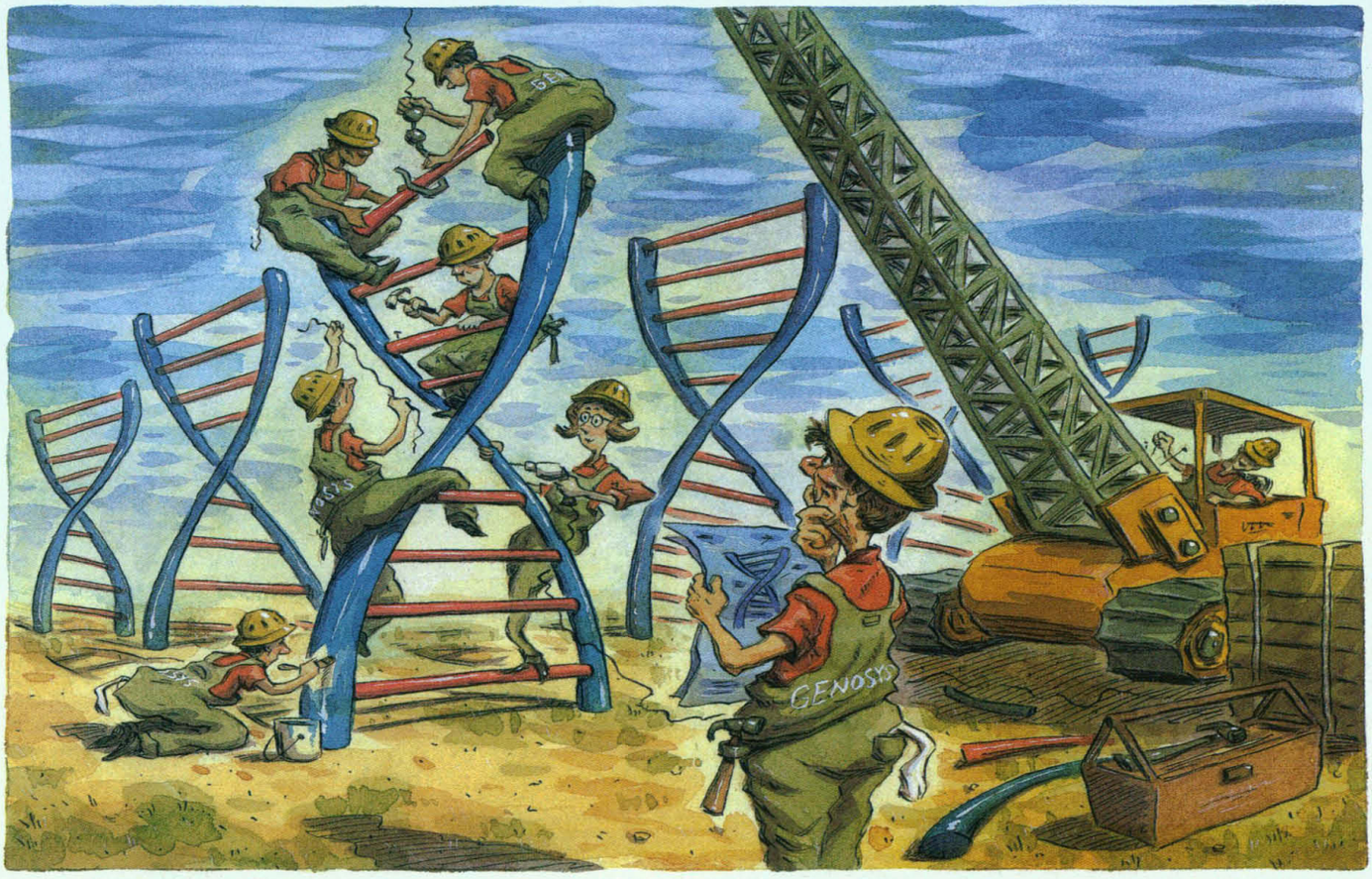

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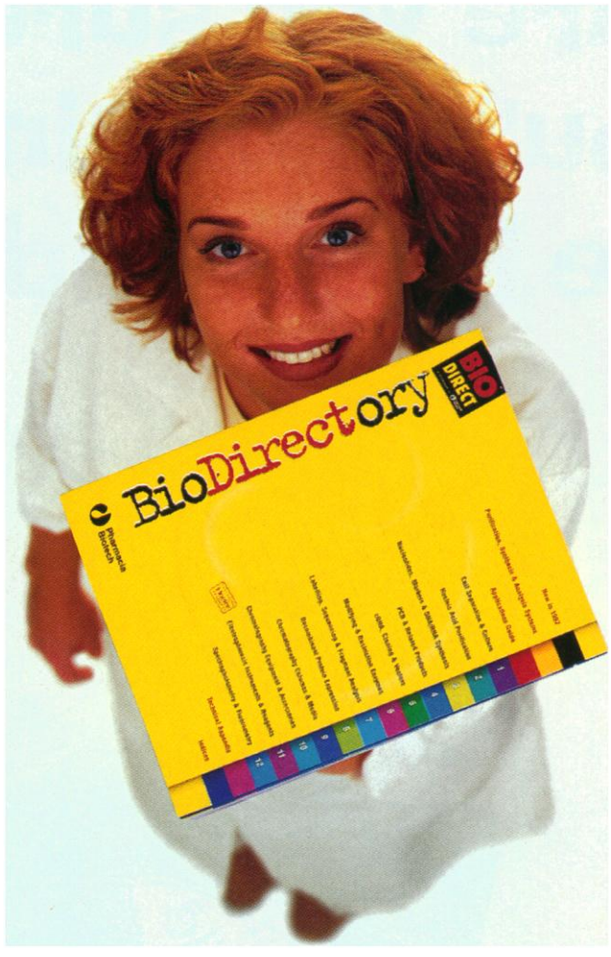

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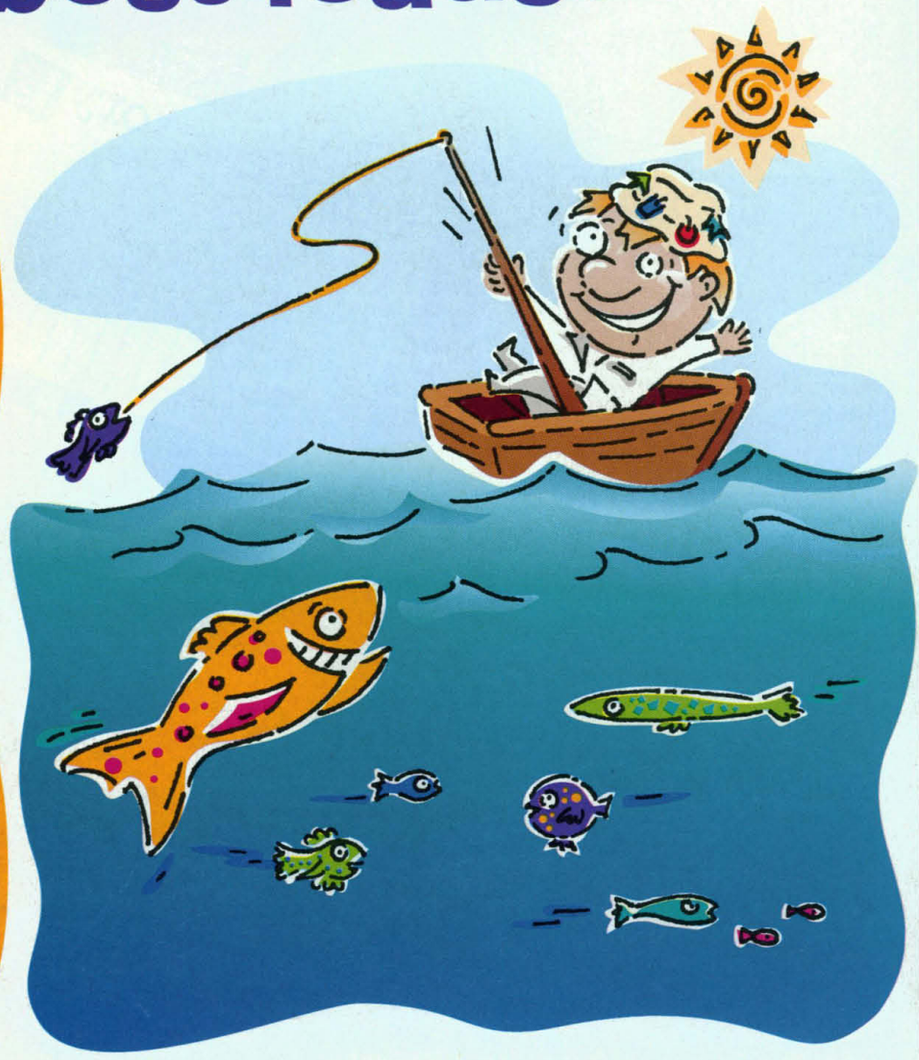

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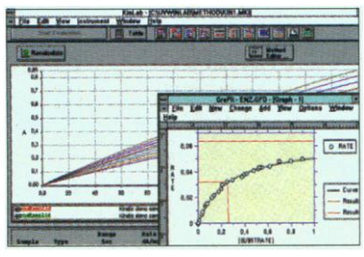

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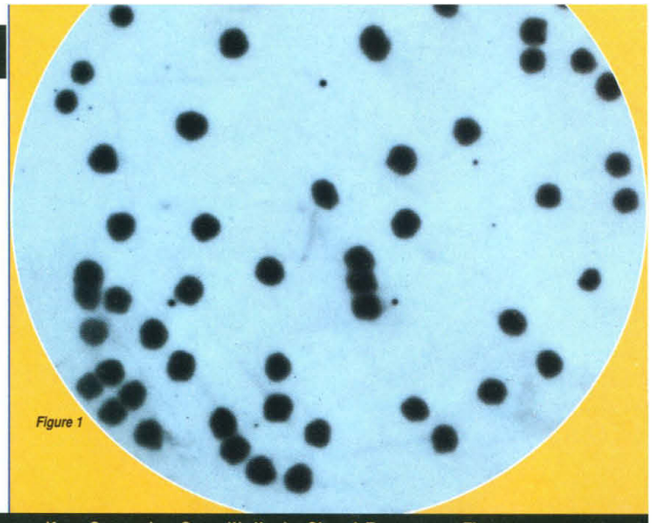

Figure 1

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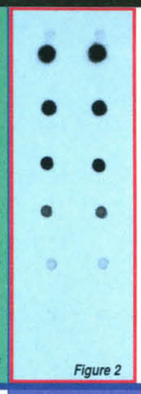

Figure 2

Figure 1. Colonies were screened for the TGF- ß1 gene with a fluorescein-labeled oligonucleotide probe and Enhanced Luminol. *This film demonstrates results obtained using the Renaissance 3'- End Labeling Fluorescein Kit with Antifluorescein-HRP (NEL823) and the detection substrate Enhanced Luminol (NEL201). Discs were exposed to Reflection film for 15 minutes.*

Figure 2. Mouse ß-actin was detected using a fluorescein-labeled ssRNA probe and ready-to-use CDP-Star. *This film demonstrates results obtained using Renaissance RNA Fluorescein Labeling Kit with Antifluorescein-AP (NEL633) in conjunction with ready-to-use CDP-Star (NEL601). Blots were exposed to Reflection film for 5 minutes.*

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Figure 3. The v-Fos gene was detected in 125 ng of blotted mouse genomic DNA in less than 5 minutes using CDP-Star. *This film demonstrates results obtained using the Renaissance Random Primer Biotin Labeling Kit with Streptavidin-AP (NEL604) in conjunction with ready-to-use CDP-Star (NEL601). Blots were exposed to Reflection film for 5 minutes.*

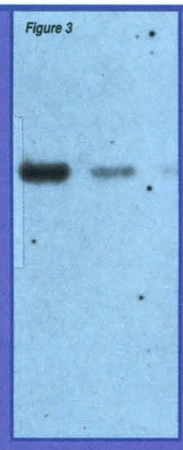

Figure 3

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Genomics's Wheelers and Dealers

Affymetrix

Santa Clara, California

Key feature: Designing DNA probe arrays using GeneChip system

Key technologies: Semiconductor fabrication techniques that put DNA sequences on glass "chips"

"Our chips allow people much easier access to genetic information. There's a lot we can do by looking at patterns."
Stephen Fodor, President ➢

Key corporate collaborators	Focus	Deal value
Hoffmann–La Roche	*H. influenzae* and *S. pneumoniae* genes	undisclosed
Merck & Co.	human gene expression	undisclosed
Glaxo Wellcome	detection of mutations	undisclosed

IPO date	Value	Share price
6 June 1996	$90 million	$15

Key players	Stock holdings (number of shares)	Salaries and other compensation
Stephen Fodor, President	153,333	$188,819 base salary
Alejandro Zaffaroni	140,000	none reported
Paul Berg	38,488	none reported

Genset

Paris

C. VIOUJARD/GAMMA LIAISON

Key feature: Identifying genes and regulatory regions of genes

Key technologies: Large-scale, high-throughput sequencing; technique for isolating "5 prime" sequences at beginning of genes (including regulatory regions); "functional polymorphism scanning" for analyzing gene variations in a population; bioinformatics

"We discover pathways with minimal benchwork."
Daniel Cohen, Chief Genomics Officer ➢

Key corporate collaborators	Focus	Deal value
Synthelabo	prostate cancer	$70.5 million
Johnson & Johnson	schizophrenia	under negotiation

IPO date	Value	Share price
5 June 1996	$86.4 million	$16

Key players	Stock holdings (number of shares)	Salaries and other compensation
Pascal Brandy, CEO	Because Genset is a foreign-based company, the U.S. Securities and Exchange Commission does not require the reporting of individual officers' stock and compensation information. The prospectus does, however, report that as a group, these three officers have options on an aggregate of 534,200 shares of stock. They also split $357,000 in compensation with seven directors (who only received "limited" amounts and "incidental" expenses).	
Marc Vasseur, Chief Biology Officer		
Daniel Cohen, Chief Genomics Officer		

Genome Therapeutics Corp.

Waltham, Massachusetts

Key feature: Sequences pathogen genomes

Key technologies: Proprietary high-throughput "multiplex" DNA sequencing; positional cloning; bioinformatics

"In bacteria, the gap between gene discovery and drug discovery is so much shorter than in humans."
Bernd Seizinger, Chief Scientific Officer ➢

Key corporate collaborators	Focus	Deal value
Astra AB	access *H. pylori* gene database	$11 million
Schering-Plough	access unspecified pathogen database	$13.3 million
Schering-Plough	asthma	$22.5 million

IPO date	Value	Share price
1982	not available	not available

Subsequent offering date	Value	Share price
15 February 1996	$39 million	$7.69

Key players	Stock holdings* (number of shares)	Salaries and other compensation*
Robert Hennessey, CEO	1,600,000	$260,000 base salary, $50,000 bonus
Bernd Seizinger	not available	not available
Philip Leder, Director	137,250	none reported

* From 16 January 1996 proxy statement

Human Genome Sciences

Rockville, Maryland

Key feature: Sells subscriptions to the Human Gene Anatomy Project, putatively the world's largest collection of cDNAs from normal and abnormal human tissues

Key technologies: Large-scale sequencing; bioinformatics

"Our database is a tool of invaluable power for asking medical questions."
William Haseltine, CEO ➢

Key corporate collaborators	Focus	Deal value
SmithKline Beecham	access to cDNA database	$125 million
Merck KGaA	access to cDNA database	$50 million
Schering-Plough	access to cDNA database	$55 million
Synthelabo	access to cDNA database	$35 million

IPO date	Value	Share price
1 December 1993	$27 million	$12

Key players	Stock holdings (number of shares)	Salaries and other compensation
William Haseltine, CEO	1,162,887	$200,000 base salary, $50,000 min. annual bonus, $9000/year car allowance, $70,000 legal and accounting fees
J. Craig Venter, TIGR	1,376,513	none reported

Incyte Pharmaceuticals

Palo Alto, California

Key feature: Sells subscriptions to Internet-accessible LIFESEQ database of cDNA sequences and expression patterns

Key technologies: Large-scale sequencing; expression analysis; bioinformatics

"In biotech before, people were staking out claims and trying to mine. [Now we're] making a business out of selling tools to miners."

Roy Whitfield, CEO ➢

Key corporate collaborators	Focus	Deal value
Pfizer	access to cDNA database	$15.75 million
Upjohn	access to cDNA database	$10 million
8 other customers		undisclosed

IPO date	Value	Share price
4 November 1993	$15 million	$7.50

Subsequent offering date	Value	Share price
8 November 1995	$32.3 million	$19

Key players	Stock holdings* (number of shares)	Salaries and other compensation*
Roy Whitfield, CEO	435,320	none reported
Randall Scott, Chief Scientific Officer	228,345	none reported

*From subsequent offering

Millennium Pharmaceuticals

Cambridge, Massachusetts

Key feature: Identifying disease genes with synergistic approaches

Key technologies: Large-scale DNA sequencing; rapid analysis of differential gene expression; positional cloning; high-throughput expression cloning; bioassays for high-throughput drug screens; bioinformatics; comparative genetics

"Genomics is a whole set of technologies, and it's going to dramatically change the pharmaceutical industry."

Mark Levin, CEO ➢

Key corporate collaborators	Focus	Deal value
Hoffmann–La Roche	obesity and type II diabetes	$44.5 million
Eli Lilly	atherosclerosis and cancer	$61 million
Astra AB	inflammatory respiratory disease	$53.3 million
American Home Products	CNS diseases	$90 million

IPO date	Value	Share price
6 May 1996	$54 million	$12

Key players	Stock holdings (number of shares)	Salaries and other compensation
Mark Levin, CEO	1,563,216	100,000 share option, $300,000 base salary, relocation expenses up to $100,000
Eric Lander, consultant	749,591	maximum $95,000/yr. fees

Myriad Genetics

Salt Lake City

Key feature: Developing predisposition tests using more than 25,000 clinical samples from large, multigenerational Utah families

Key technologies: High-speed gene sequencing; positional cloning; bioinformatics

"There's a significant opportunity in genetics predisposition testing rather than in developing therapeutics on our own, which is a much riskier proposition."

Peter Meldrum, CEO ➢

Key corporate collaborators	Focus	Deal value
Ciba-Geigy	cardiovascular disease	$25 million
Bayer	obesity, osteoporosis, and asthma	$25 million
Eli Lilly	breast cancer	undisclosed

IPO date	Value	Share price
5 October 1995	$46.8 million	$18

Key players	Stock holdings (number of shares)	Salaries and other compensation
Peter Meldrum, CEO	609,657	$175,355 base salary, $90,000 bonus
Mark Skolnick, VP of R&D	657,694	$90,182 base salary, $100,000 bonus
Walter Gilbert, Vice Chair	304,454	$10,000 annual retainer

Sequana Therapeutics

La Jolla, California

Key feature: Has access to more than 30,000 DNA samples from individuals and families affected by specific diseases

Key technologies: Positional cloning; high-throughput DNA sequencers and analyzers; high-throughput cell-based drug screens; bioinformatics; comparative genetics

"All biotechnology companies, by dint of the power of genomics, will have to tailor their research programs toward genomics."

Kevin Kinsella, CEO ➢

Key corporate collaborators	Focus	Deal value
Boehringer Ingelheim	asthma	$32.5 million
Glaxo Wellcome	type II diabetes	undisclosed
Corange	osteoporosis	$21 million

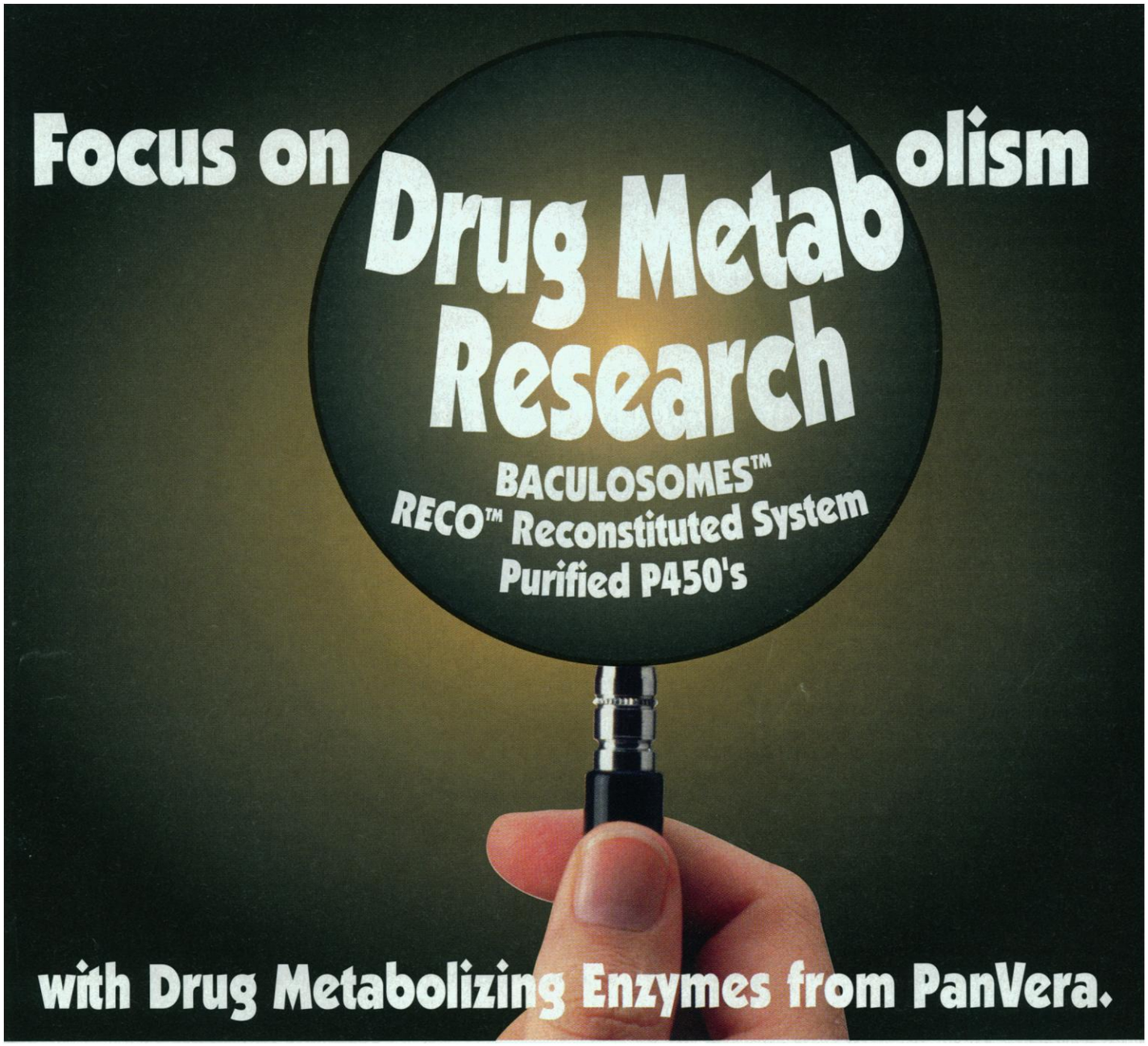
IPO date	Value	Share price
31 July 1995	$18 million	$9

Subsequent offering date	Value	Share price
6 March 1996	$30.4 million	$19

Key players	Stock holdings (number of shares)	Salaries and other compensation
Kevin Kinsella, CEO*	208,333	$250,000 base salary
Timothy Harris, Chief Technical Officer	33,333	$176,500 base salary, $62,582 moving expenses

* Kinsella also is managing general partner of Avalon Ventures, which has 198,305 shares of Sequana stock.

Unless otherwise noted, all stock and compensation information comes from company prospectuses filed for initial public offerings (IPOs), and the value of all collaborative deals listed is the total potential revenue, excluding milestone and royalty payments if products are developed. Note that the quoted stock prices likely have changed significantly as the market fluctuates daily, and that stock holdings may include options that have yet to become vested.



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PanVera's BACULOSOMES are simple to use and require no additional protein components for biotransformation activity. These membranes are produced from insect cells co-infected with a baculovirus vector expressing both a recombinant human P450 isoform and rabbit NADPH-P450 oxidoreductase. BACULOSOMES exhibit higher specific activity than human liver microsomes and are competitively priced. *BACULOSOMES currently available:* 2C19, 2D6, 3A4, 3A4+b_5.

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RECO™ System
Purified P450's are also available in PanVera's ready-to-use "Mix & Metabolize" RECO System, which includes a complete enzyme mix and separate reaction buffer. This format greatly simplifies the use of purified cytochrome P450 isozymes with their associated proteins, making them as easy to use as microsomes but with the inherent advantage of using purified proteins. *RECO Systems currently available:* 3A4, 1A2.

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PanVera also offers other recombinant human enzymes including cytochrome b_5, NADPH-P450 oxidoreductase, UGT 1*1, and GST's. Additional Drug Metabolizing Enzymes are currently under development.

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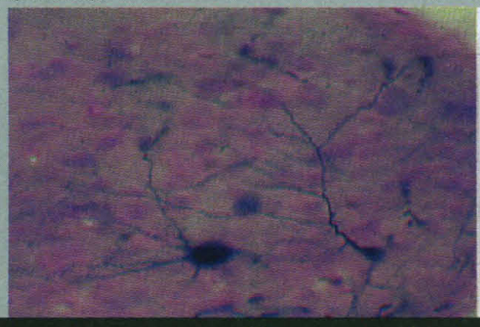
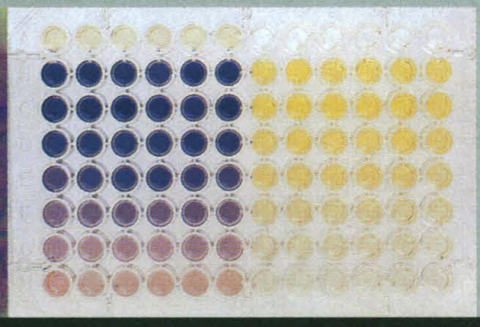
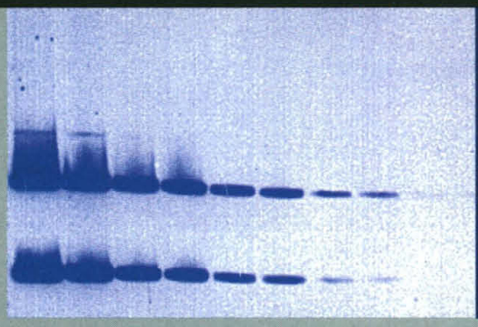
Biotinylated dextran injected iontophoretically into the auditory cortex of rat brain to label somata and neuronal profiles. Tissue treated with KPL's Streptavidin-Peroxidase, followed with TrueBlue™ Peroxidase Substrate. Counterstained with Contrast RED. Photographed using a 3-dimensional light microscope.



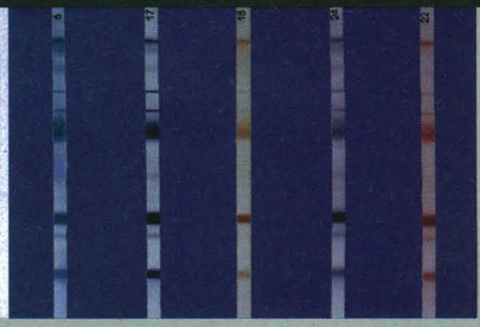
Microplate wells coated with 1.5 µg/ml of rabbit IgG excepting row A, then blocked. Alkaline phosphatase-labeled goat anti-rabbit IgG (H+L) added to row A at a concentration of 50 ng/ml, with a dilution series of conjugate ending in row H at a concentration of 2.5 ng/ml. Incubated for 20 minutes with KPL's BluePhos™ Substrate (left side) and *p*NPP Phosphatase Substrate (right side).



Why use radioactivity when you can get results like this without it?



Southern Blot of *Eco*R 1 digested pE1.4 detected using KPL's Biotin Detection Kit. Lane 1: 10 ng pE1.4 Lanes 2-6: 5 ng, 1 ng, 500 pg, 100 pg, 50 pg. Lanes 7-11: 10 pg, 5 pg, 1 pg, 0.5 pg, 0.1 pg.



Western Blots of HIV-1 viral lysate electroblotted onto nitrocellulose membrane. Immunodetection with HIV-positive human serum followed by enzyme-labeled antibody. Immunodetected with appropriate KPL substrate.

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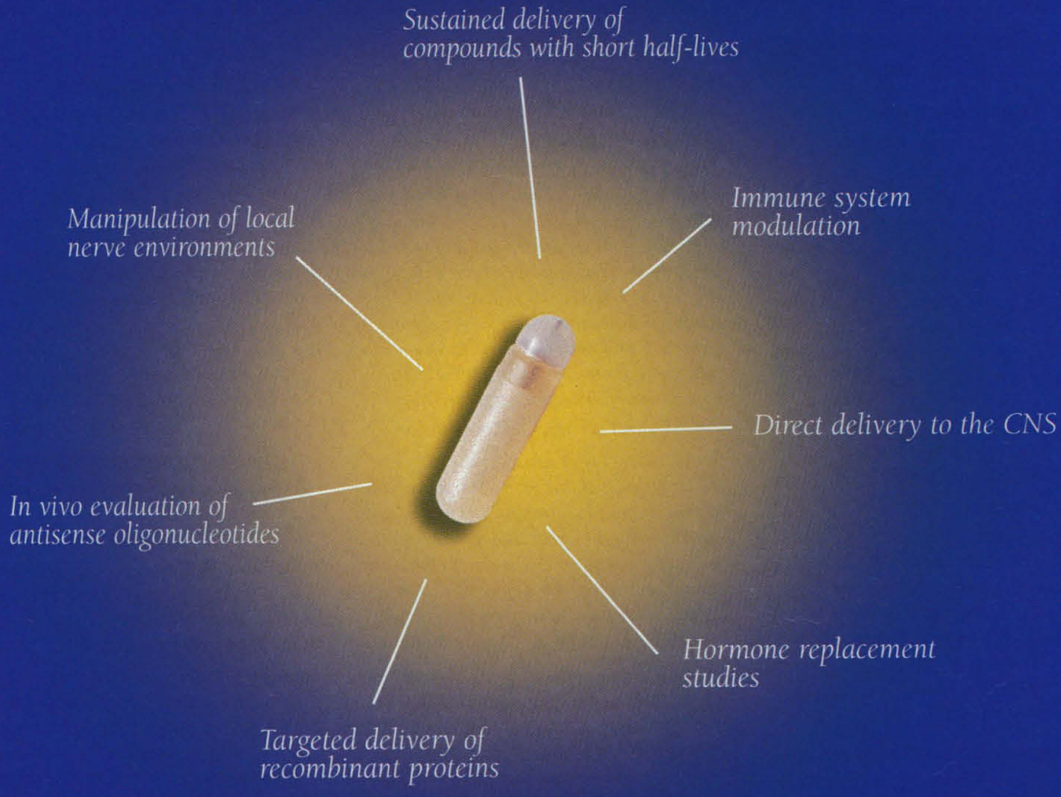

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