27 November 1998

Science

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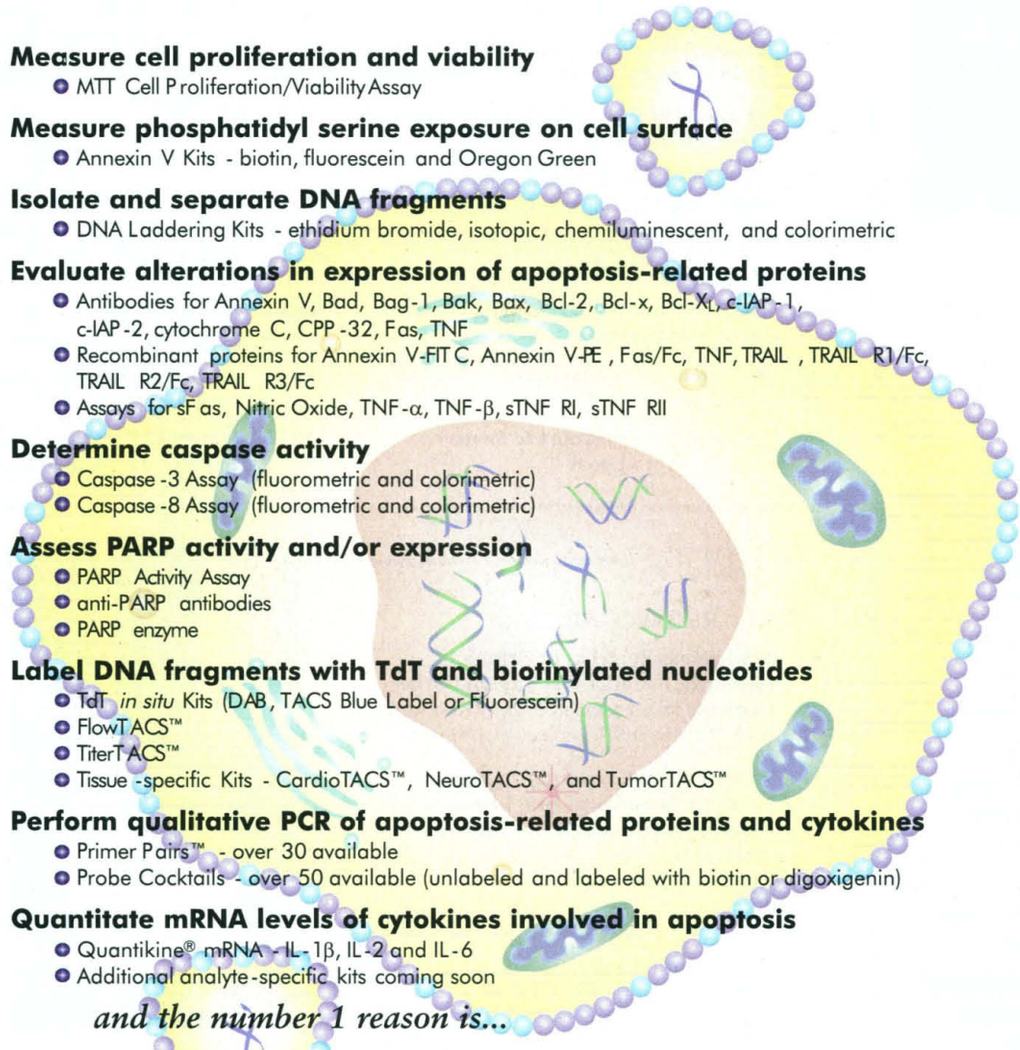
Top 10 Reasons To Use R&D Systems' Apoptosis Reagents

from the home office in Minneapolis, MN



10. **Measure cell proliferation and viability**
    - MTT Cell Proliferation/Viability Assay

9. **Measure phosphatidyl serine exposure on cell surface**
    - Annexin V Kits - biotin, fluorescein and Oregon Green

8. **Isolate and separate DNA fragments**
    - DNA Laddering Kits - ethidium bromide, isotopic, chemiluminescent, and colorimetric

7. **Evaluate alterations in expression of apoptosis-related proteins**
    - Antibodies for Annexin V, Bad, Bag-1, Bak, Bax, Bcl-2, Bcl-x, Bcl-X_L, c-IAP-1, c-IAP-2, cytochrome C, CPP-32, Fas, TNF
    - Recombinant proteins for Annexin V-FITC, Annexin V-PE, Fas/Fc, TNF, TRAIL, TRAIL R1/Fc, TRAIL R2/Fc, TRAIL R3/Fc
    - Assays for sFas, Nitric Oxide, TNF-α, TNF-β, sTNF RI, sTNF RII

6. **Determine caspase activity**
    - Caspase-3 Assay (fluorometric and colorimetric)
    - Caspase-8 Assay (fluorometric and colorimetric)

5. **Assess PARP activity and/or expression**
    - PARP Activity Assay
    - anti-PARP antibodies
    - PARP enzyme

4. **Label DNA fragments with TdT and biotinylated nucleotides**
    - TdT *in situ* Kits (DAB, TACS Blue Label or Fluorescein)
    - FlowTACS™
    - TiterTACS™
    - Tissue-specific Kits - CardioTACS™, NeuroTACS™, and TumorTACS™

3. **Perform qualitative PCR of apoptosis-related proteins and cytokines**
    - Primer Pairs™ - over 30 available
    - Probe Cocktails - over 50 available (unlabeled and labeled with biotin or digoxigenin)

2. **Quantitate mRNA levels of cytokines involved in apoptosis**
    - Quantikine® mRNA - IL-1β, IL-2 and IL-6
    - Additional analyte-specific kits coming soon

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VOLUME 282 27 NOVEMBER 1998 NUMBER 5394

Science

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COVER A carpel-bearing stem of a Jurassic angiosperm (enlarged about 5.5 times), *Archaefructus* gen. nov., from the lower Yixian Formation near Beipiao, Liaoning Province, northeast China. Carpels enclosing ovules define the angiosperms and are preserved in this fossil. The age of this fossil pushes back the origins of angiosperms by about 20 million years. [Photo: David Dilcher and Ge Sun]

1616
Mother knows best

NEWS

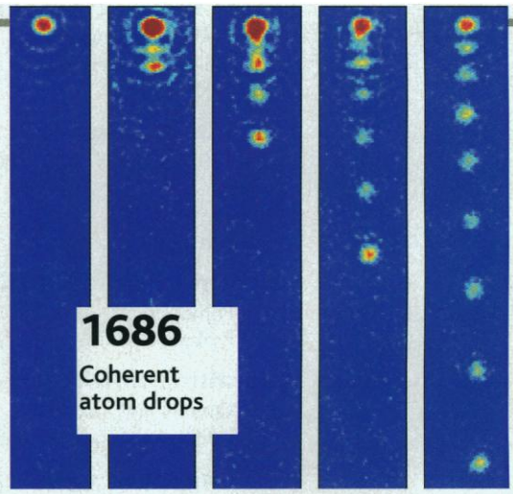
NEWS OF THE WEEK

NEWS FOCUS

RESEARCH

RESEARCH ARTICLES

REPORTS



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SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals Mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices. Domestic individual membership and subscription (51 issues): $108 ($60 allocated to subscription). Domestic institutional subscription (51 issues): $295. Foreign postage extra: Mexico, Caribbean (surface mail) $55; other countries (air assist delivery) $90. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. IPM #1069624. **Printed in the U.S.A.**

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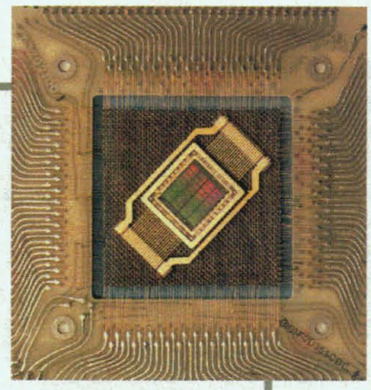

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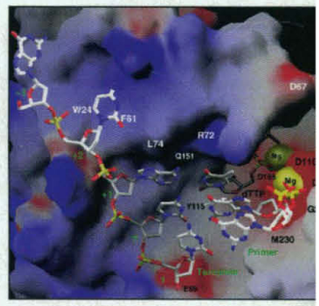

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THE MJ RESEARCH NOTEBOOK

Volume VIII...No. 4 *A Bulletin of Technological Advance in Molecular Biology* *Winter 1998*

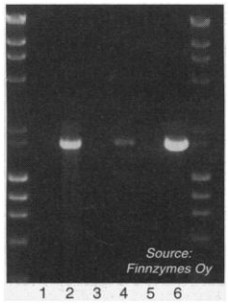
AMPLIFY GC-RICH TEMPLATES WITH EASE

ENZYME BLASTS THROUGH SECONDARY STRUCTURES

Some templates are difficult to amplify because they are GC-rich or contain long complementary areas that easily form loops. These secondary structures can prevent primer annealing and/or DNA synthesis, and thus they inhibit PCR and other amplification reactions.

DyNAzyme EXT is a particularly capable enzyme mix for driving amplification reactions in these tough circumstances. But sometimes, even EXT isn't enough. Fortunately, the enzyme is also tolerant of extra additives.

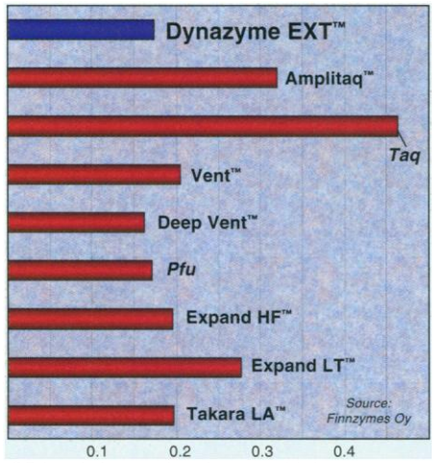
Often special "helping" solutions are employed to change the melting characteristics of DNA and thus minimize the effects of secondary structure. These additives may be DMSO, formamide, glycerol, betaine, etc. EXT was tested alongside of two market-leading enzymes with and without their proprietary helping solutions. The result? Just look at the gel—— DyNAzyme EXT with 5% DMSO (an ordinary lab reagent) was significantly more effective in amplifying a 69% GC-rich template than either of the competing enzymes with their proprietary solutions.



PCR on TGF-ß1 1.9kb region (69% GC-rich)

#1 "Q" *taq*, #2 "Q" *taq*+sol.
#3 "C" *taq*, #4 "C" *taq*+sol.
#5 EXT, #6 EXT+5% DMSO

DyNAzyme EXT™ Polymerase Exhibits Extraordinary Fidelity



OD(450), lower signal means higher accuracy

Fidelity Assayed in Actual PCR Reactions

The data above represent relative fidelity among a number of polymerases. It was collected using the immobilized mismatch binding protein method (IMBP)‡. This technique, which detects errors through the binding of a repair protein, does not yield absolute numbers for error rates, but it is extremely effective in showing relative performance. It assays accuracy during actual PCR by measuring the number of accumulated errors in the final product, and it is able to detect almost all common mistakes. For more info, see www.genecheck.com.

‡Wagner, R. & Dean, A. 1998. *The use of immobilized mismatch binding protein for the optimization of PCR fidelity* in "PCR Methods Manual," Innis M. Gelfand, D. and Sninsky, J. eds, in press

BROAD TOLERANCE FOR VARYING REACTION CONDITIONS

Get the Best of Both Worlds– Accuracy & Robust Reactions

WATERTOWN, Mass. — Since the spring of 1998, MJ RESEARCH has distributed the PCR-licensed DNA polymerases made by Finnzymes Oy of Finland. These enzymes have their origin in the thermophile *T. brockianus*, and they exhibit many superior properties to *Taq* polymerase in driving PCR reactions (especially in thermal stability and yield).

However, one question that was frequently asked is, "What's the fidelity compared to *Taq*?" Unfortunately, determining error rates is very laborious and condition dependent, and making comparisons among enzymes is not easily done. But now solid data exists—and the results are so good, the Finns insisted on repeating the experiments over and over again.

The assay used was IMBP *(see accompanying article)*, and DyNAzyme EXT* was particularly outstanding in its fidelity characteristics. EXT is a cocktail with a small amount of proofreading enzyme, and it is great for long PCR, high-fidelity TA cloning, and difficult templates. Yet in this fidelity assay, it performed as well or better than every other polymerase tested—including proofreading enzymes considered to be the "gold standards" of accuracy! But unlike those enzymes, EXT has the finesse to amplify templates as long as 40kb, the versatility to amplify templates that are high in GC content, as well as the robustness to withstand widely varying reaction conditions.

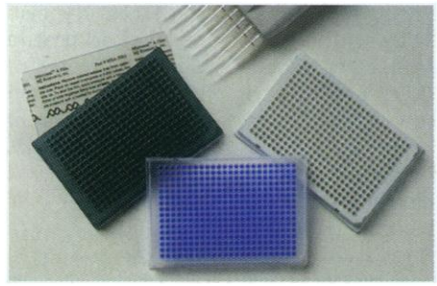
All DyNAzyme enzymes come licensed by Hoffmann-LaRoche to perform PCR reactions in research.** DyNAzyme is available as native enzyme, recombinant enzyme, or as the EXT cocktail. All are available separately or in kits, and they come with a variety of buffers.

384-well Format Comes Into Its Own

Plates Now Flatter & Bar Coded

MJ Research has been involved in the development of the 384-well format since 1993. In fact, the V-well design generally used in thermal cycling was developed by MJ engineers. It is a true 4x96-well configuration, which allows use of the same dispensing/harvesting equipment as with 96 wells (the frame is just shifted).

The newly improved Microseal 384 plate features a rigid, robot-friendly design with an industry-standard footprint and locator holes for secure handling. The flatter upper surface provides more reliable automated liquid dispensing, and the plates are much less likely to stick in the block after cycling. Serialized bar code labels (code39) are a new, low-cost option.



384-well plates of polypropylene plastic, now much improved for automated applications

*EXT licensed under US Pat. 5,436,149 owned by TaKaRa Shuzo Co. Ltd.

** Purchase of DyNAzyme polymerase is accompanied by a limited license to use it in the Polymerase Chain Reaction (PCR) process for research in conjunction with a thermal cycler whose use in the automated performance of the PCR process is covered by the up-front license fee, either by payment to Perkin-Elmer or as purchased, i.e. an authorized thermal cycler.

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PERIODIC TABLE IN THE SKY

Despite the key role that aerosols play in ozone destruction and global cooling, most measurements have been performed on retrieved samples, which can become contaminated or can undergo aggregation. Murphy *et al.* (p. 1664) report in situ aerosol data from measurements aboard research aircraft that span the troposphere and stratosphere at altitudes between 5 and 19 kilometers. More than 28,000 individual particles were characterized in terms of their size and chemical composition. At least 45 different elements are present in these particles, including meteoritic material and mercury in stratospheric aerosol and organic material in tropospheric aerosol. Such measurements may allow the origins of particular types of aerosols to be traced.

HUMAN INFLUENCE ON CLIMATE

Efforts have been made to identify the human influence on climate during the 20th century, but controversy persists whether natural variability and anthropogenic forcing have been attributed adequately in these studies. Wigley *et al.* (p. 1676) analyze the auto- and cross-correlation structure of hemispheric mean temperature from observations and from several different climate model simulations. They show that significant external forcing exists that cannot be attributed purely to solar forcing but rather to a combination of solar and anthropogenic forcing. The study provides strong evidence for significant anthropogenic forcing on global climate.

LOW-DIELECTRIC MIRRORS

Metals make fine mirrors in many wavelength ranges, but for certain applications low-dielectric materials may be preferred. Fink *et al.* (p. 1679) show theoretically that stacking alternating layers of materials with different dielectric constants can produce materials that are reflectors over a particular range of wavelengths, and they demonstrate high reflectivity for wavelengths from 10 to 15 micrometers with a material made from alternating layers of polystyrene and tellurium. This approach opens up the possibility of tuning the wavelength range of coatings for transparency and reflectivity.

QUANTUM INTERFERENCE OF ATOMIC TUNNEL ARRAYS

Atoms can be cooled and trapped to a fraction of a degree above absolute zero to form an unusual state of matter, a Bose-Einstein condensate (BEC). Manipulation of the BEC can allow quantum effects to be observed macroscopically. Anderson and Kasevich (p. 1686; see the Perspective by Burnett) allowed a rubidium BEC to fall gravitationally through a periodic array of laser traps (standing waves). The trapped atoms tunnel coherently through all of these potential wells created by the laser standing waves at the same time. The interference of the tunneling atoms manifests itself as a train of phase-coherent atomic pulses. This behavior is effectively that of a mode-locked atom laser.

A DIFFERENT TWIST

Polyacetylene, the simplest linear conjugated polymer, is of particular interest for electrical applications because of its high conductivity upon doping. However, processing of these polymers has proved difficult and has limited its applications. Akagi *et al.* (p. 1683) show that by performing an existing synthetic protocol in a chiral nematic liquid crystal environment, polyacetylene films form that contain helical fibrils consisting of bundles of acetylene chains. Iodine doping led to high conductivities. These helical structures may find application as electrically conducting molecular wires and may also have interesting magnetic and optical properties.

EARLY BLOOMERS

The origination of angiosperms (flowering plants) impacted the evolution of insects and other animals and greatly affected Earth's climate (particularly the CO_2 budget). Angiosperms have typically been thought to have arisen in the Cretaceous, but Sun *et al.* (p. 1692; see the cover and the Perspective by Crepet) now describe an angiosperm from probable Jurassic rocks in China that may extend their origins back several tens of millions of years.

HIV-1 REVERSE TRANSCRIPTASE IN ACTION

The reverse transcriptase (RT) enzyme of HIV-1 (human immunodeficiency virus–1) copies the viral genome into DNA that can then be integrated into the host cell's genome. Although inhibitors of the RT have been a prime target for antiviral therapy, mutations confer resistance to the RT inhibitors currently in use. Huang *et al.* (p. 1669; see the news story by Balter) present the crystal structure of HIV-1 RT in complex with both the double-stranded DNA template-primer and the deoxynucleoside triphosphate substrate. The enzyme does not specifically register to the double-stranded DNA, which often leads to poor crystallization; this problem was overcome by covalently linking the DNA to RT. The active site structure suggests how mutations can reduce sensitivity to inhibitors and cause cross-resistance.

THE FALL AND RISE OF THE PRAIRIE CHICKEN

Understanding the consequences of small population size is essential for conserving biodiversity. Westemeier *et al.* (p. 1695; see the Perspective by Soulé and Mills) chart the decline of a once common grassland bird of the midwestern United States—the greater prairie chicken—by demonstrating the links between small population size, isolation, fitness loss, and decreased genetic variation. They also report the probable saving of the population by supplementing their numbers from large, genetically diverse populations.

CLOSING THE CYCLE

Progression through the cell cycle is governed in part by the anaphase promoting complex, which causes the controlled degradation of kinases and phosphatases that are involved in orchestrating DNA replication and cell division. Zachariae *et al.* (p. 1721) describe a protein, Hct1, that controls the activity of the anaphase promoting complex and restricts its activity to the correct phase of the cell cycle.

CALCIUM AND NERVE GROWTH

Calcium has an important regulatory role in control of growth and navigation at the tip of developing or regenerating nerve cells. However, the relative contributions of Ca^{2+} that enter through channels in the plasma membrane versus Ca^{2+} released from internal stores has not been established. Takei *et al.* (p. 1705) found that type 1 inositol 1,4,5-trisphosphate recep-

CONTINUED ON PAGE 1611

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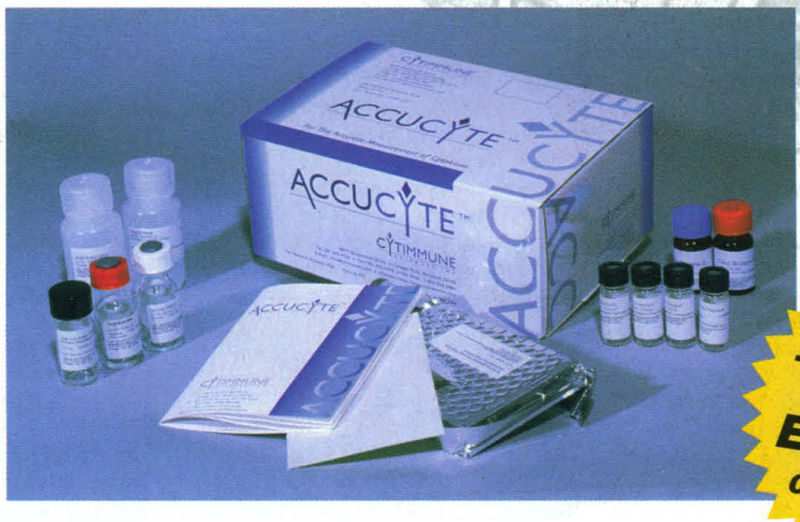

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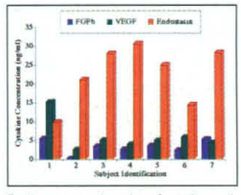

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 1609

tor (IP_3R), a channel that releases Ca^{2+} from intracellular stores, was abundantly expressed in neurons from chick dorsal root ganglion. Inhibition of Ca^{2+} release through IP_3Rs caused growth arrest and retraction of neurites. Proper neurite extension appears to require release of Ca^{2+} from intracellular stores through the IP_3R, probably in coordination with influx of extracellular Ca^{2+}.

RESPONDING TO BLUE LIGHT

The responses of plants to red and blue light involve a cascade of receptors and other proteins that translate the light signal into a growth response. Now, Christie *et al.* (p. 1698) elucidate further the transduction of the blue light signal into the physiological response. The protein encoded by the *NPH1* locus in *Arabidopsis* binds a flavin chromophore and responds to blue light with increased autophosphorylation, thus clarifying the identity of the chromophore and the initial steps in response to blue light.

GRANTING IMMUNE PRIVILEGE

Some sites in the body, such as the anterior chamber of the eye, are "immune privileged"—immune responses do not take place. These tissues were thought to be protected by their constitutive expression of Fas ligand (FasL), which induced apoptosis in meandering T cells. However, in many experimental systems where FasL is inserted as a protective element, inflammation is incited. Chen *et al.* (p. 1714) found that FasL can activate granulocytes to kill other cells. Fluid from the eye inhibits this killing—and the active agent appears to be transforming growth factor–β (TGF-β). TGF-β could prevent the rejection of tumors that was instigated by FasL in vivo. Thus, immune-privileged sites may require FasL to kill the T cells and TGF-β to thwart the inflammation.

PHAGOCYTOSIS TWO WAYS

Cells such as macrophages ingest foreign particles through phagocytosis. Receptor-particle interactions lead to progressive wrapping of particles by the cell membrane, which are then internalized for subsequent degradation. The process requires large morphological changes in the cell to accommodate the particle. Caron and Hall (p. 1717) examined the role of a family of proteins that control the actin cytoskeleton. Cells can use two different mechanisms to promote actin rearrangment during phagocytosis, which may explain the varied cellular responses to phagocytosis mediated by different cell surface receptors.

CETACEAN CULTURE

Is cultural evolution responsible for the markedly low levels of mitochondrial diversity in matrilineal species of whales? As Whitehead reports (p. 1708; see the news story by Vogel), females of these species, which include pilot, sperm, and killer whales, spend their entire lives with close female relatives under circumstances conducive to cultural development, such as a large body size, low travel costs, dispersed and patchy food sources, and the efficient transmission of sound. How would this cultural inheritance—defined as information learned from the same species that causes variation in behavior—affect mitochondrial diversity? Whitehead proposes that the selection of particular cultural traits causes an incidental reduction in diversity at neutral linked genetic loci.

TECHNICAL COMMENT SUMMARIES

Biomass Decline in Amazonian Forest Fragments

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/282/5394/1611a

W. F. Laurance *et al.* (Reports, 7 Nov. 1997, p. 1117) found that fragments of the rain forest in the Amazon experienced a large loss of above-ground tree biomass that was not offset by recruitment of new trees.

D. Cowles comments that trees of less than 10 centimeters in diameter were excluded from the analysis, which may have introduced "a bias toward measuring losses while undersampling the gains that partly offset the losses." J. B. Kauffman *et al.* also state that the data in the report "seem inadequate to ascertain losses of total above-ground biomass and carbon pools." Data from their tropical forest plots in Brazil show "a statistically significant negative correlation between the understory:overstory biomass ratio and the overstory tree biomass."

In response, Laurance *et al.* provide "estimated above-ground dry biomass for small trees and lianas (woody vines) in the central Amazon." They state that the effects described in the comments "are likely to be of limited importance" and conclude that "biomass collapse in forest fragments is a real—and worrisome—phenomenon."

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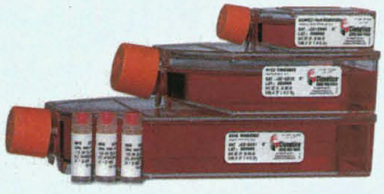

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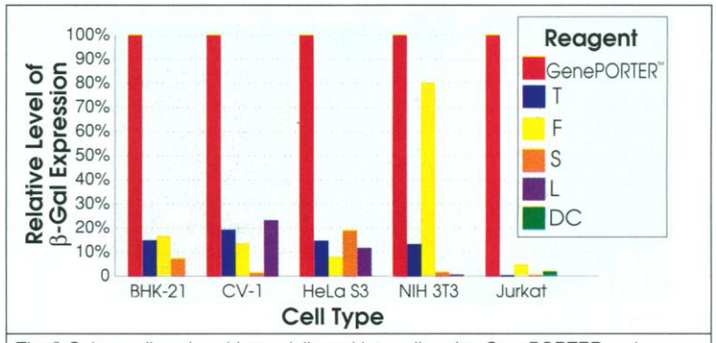

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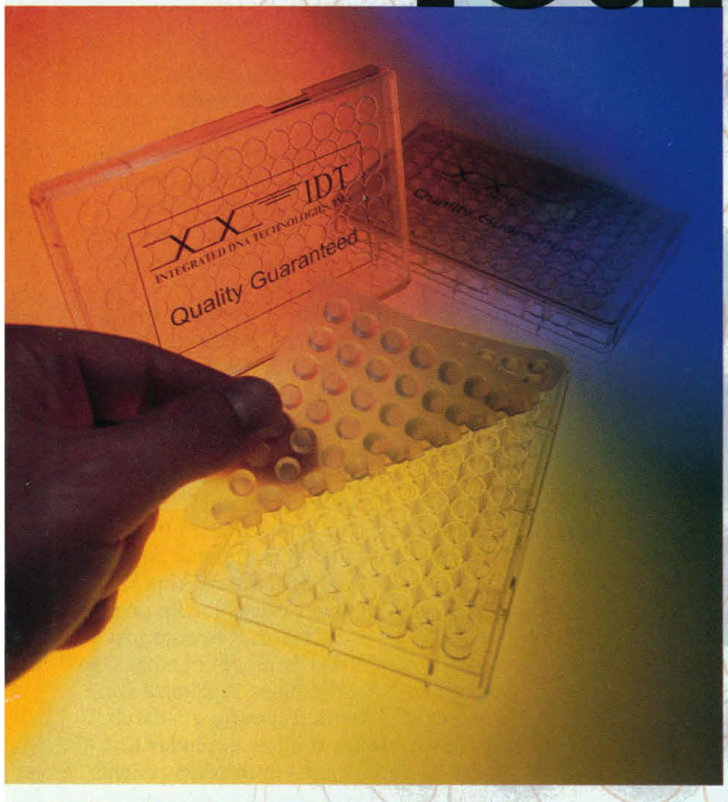

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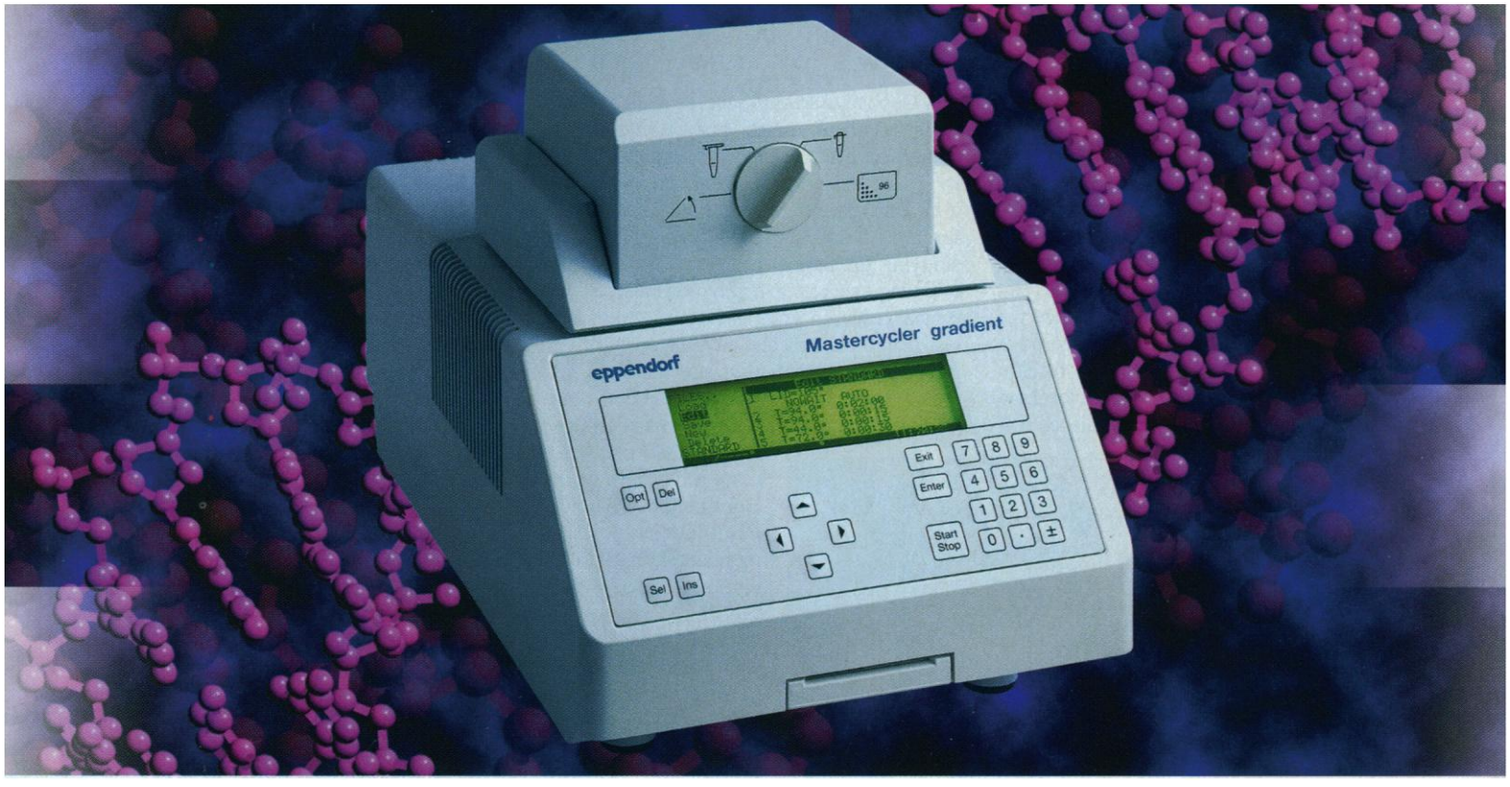

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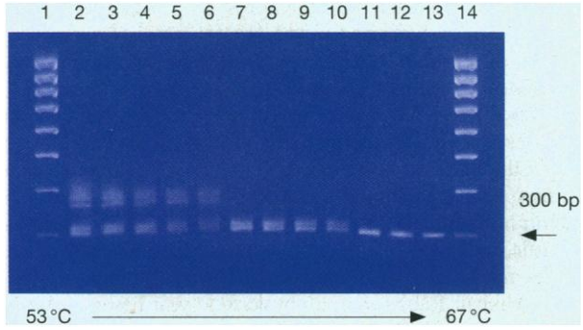

● Experimental determination of optimal annealing temperature. The calculated primer annealing temperature was 56.5 °C, the actual annealing temperature is 63.5 °C. The ribosomal spacer region of mycoplasms from H9 cell cultures was amplified.

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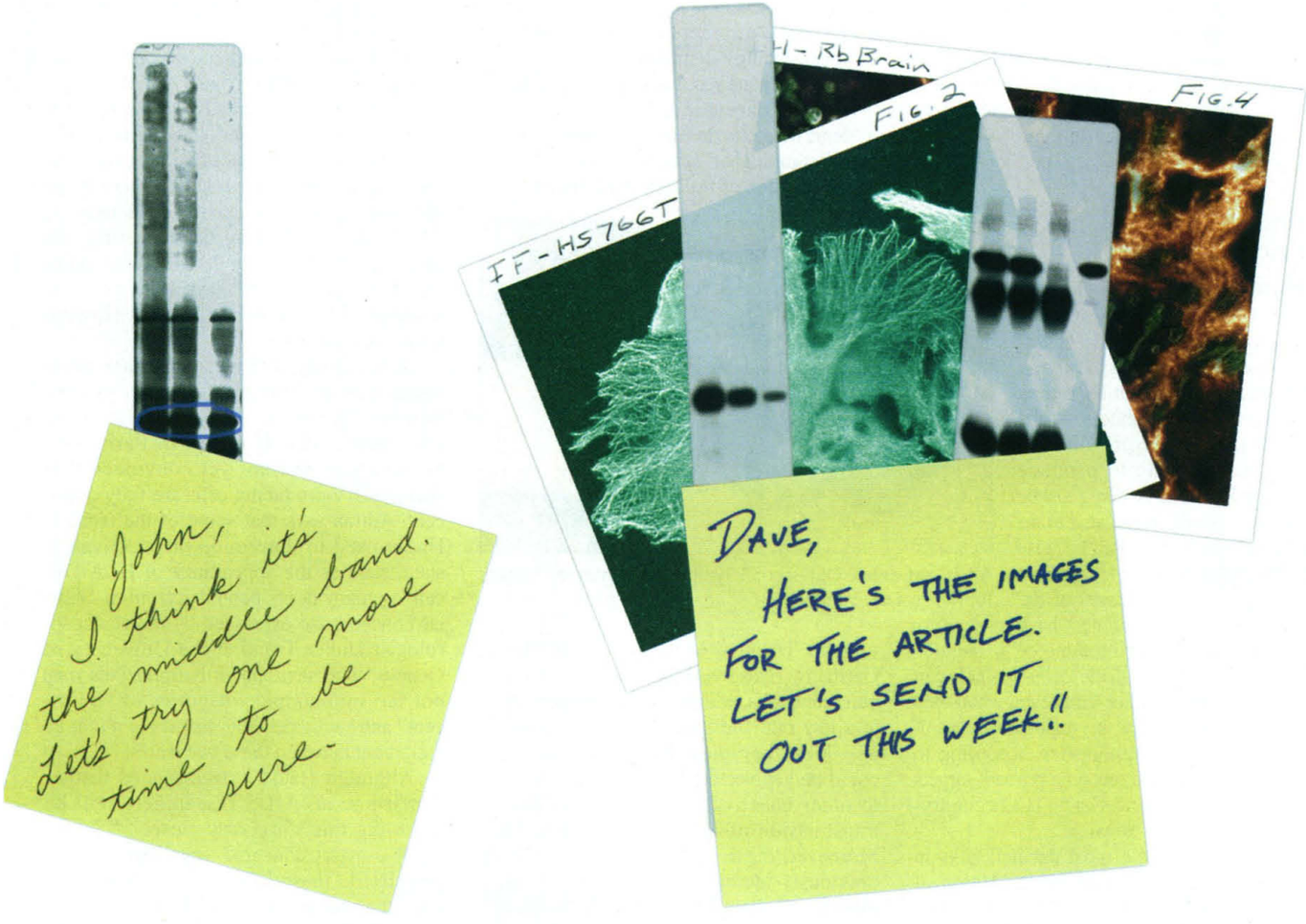

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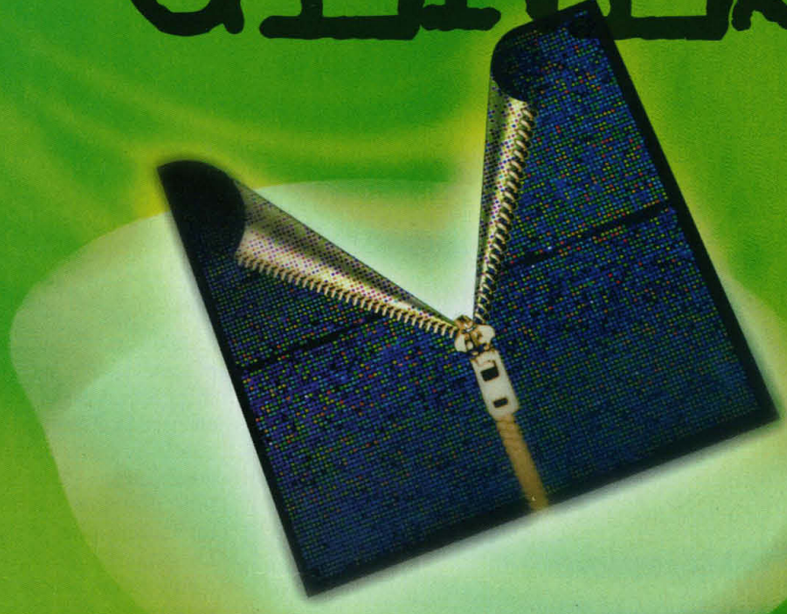

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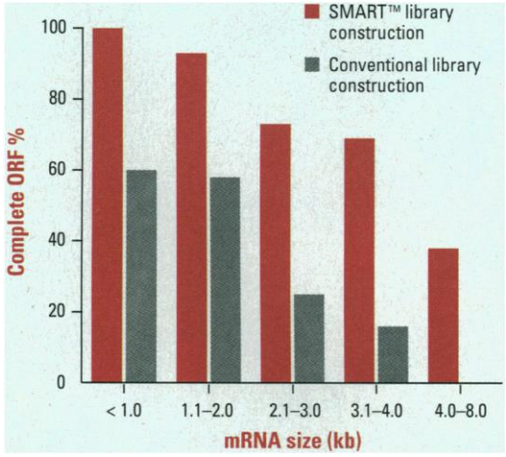

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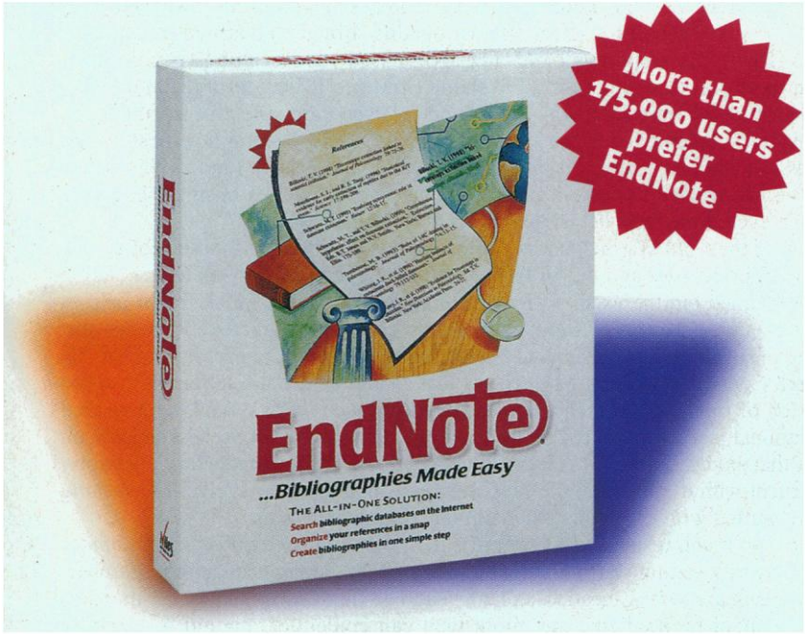

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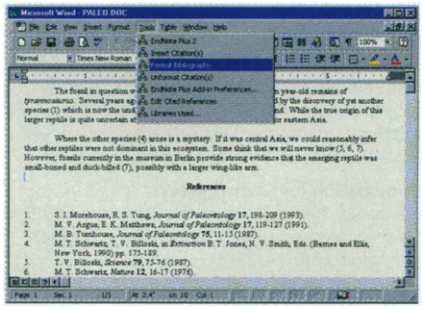

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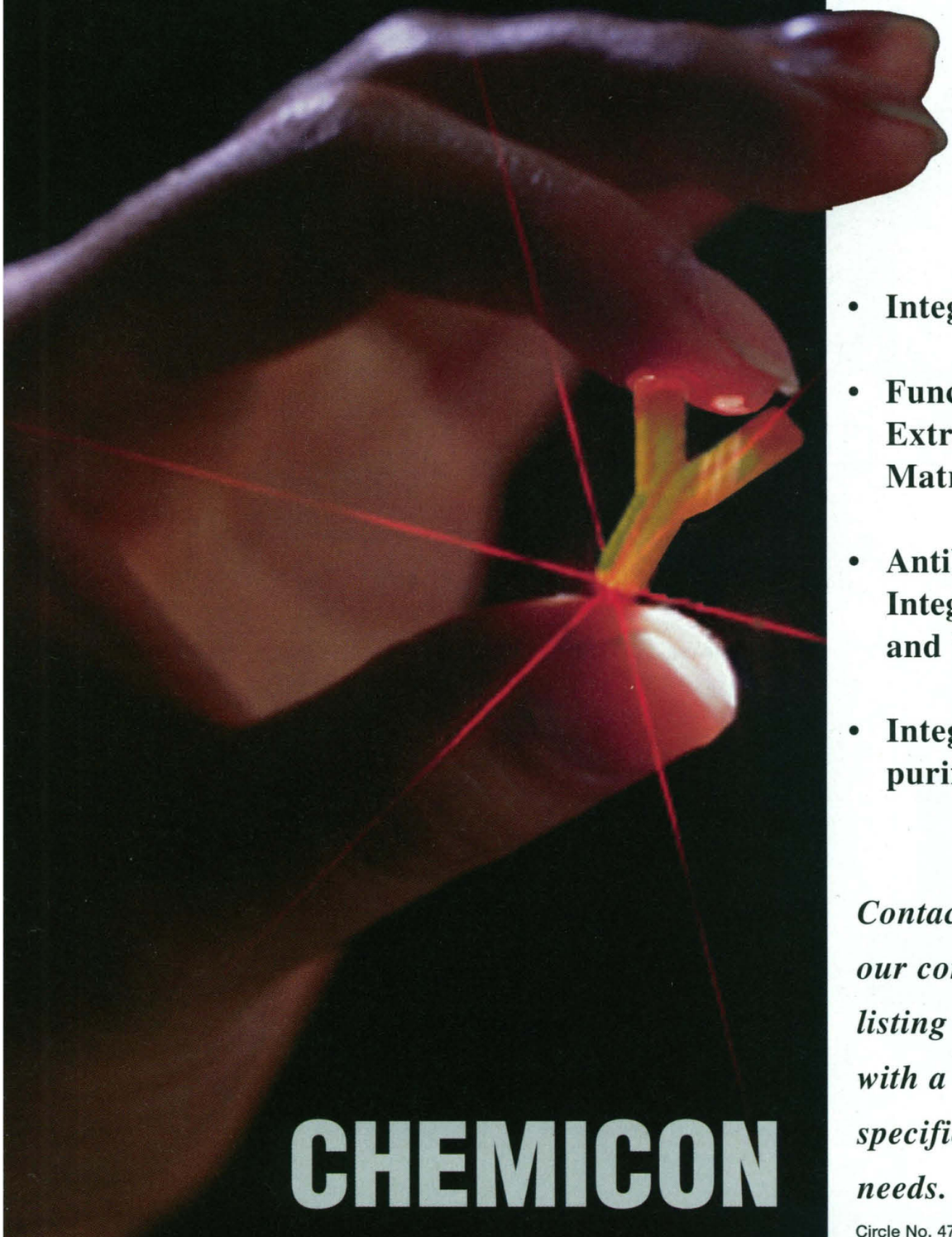

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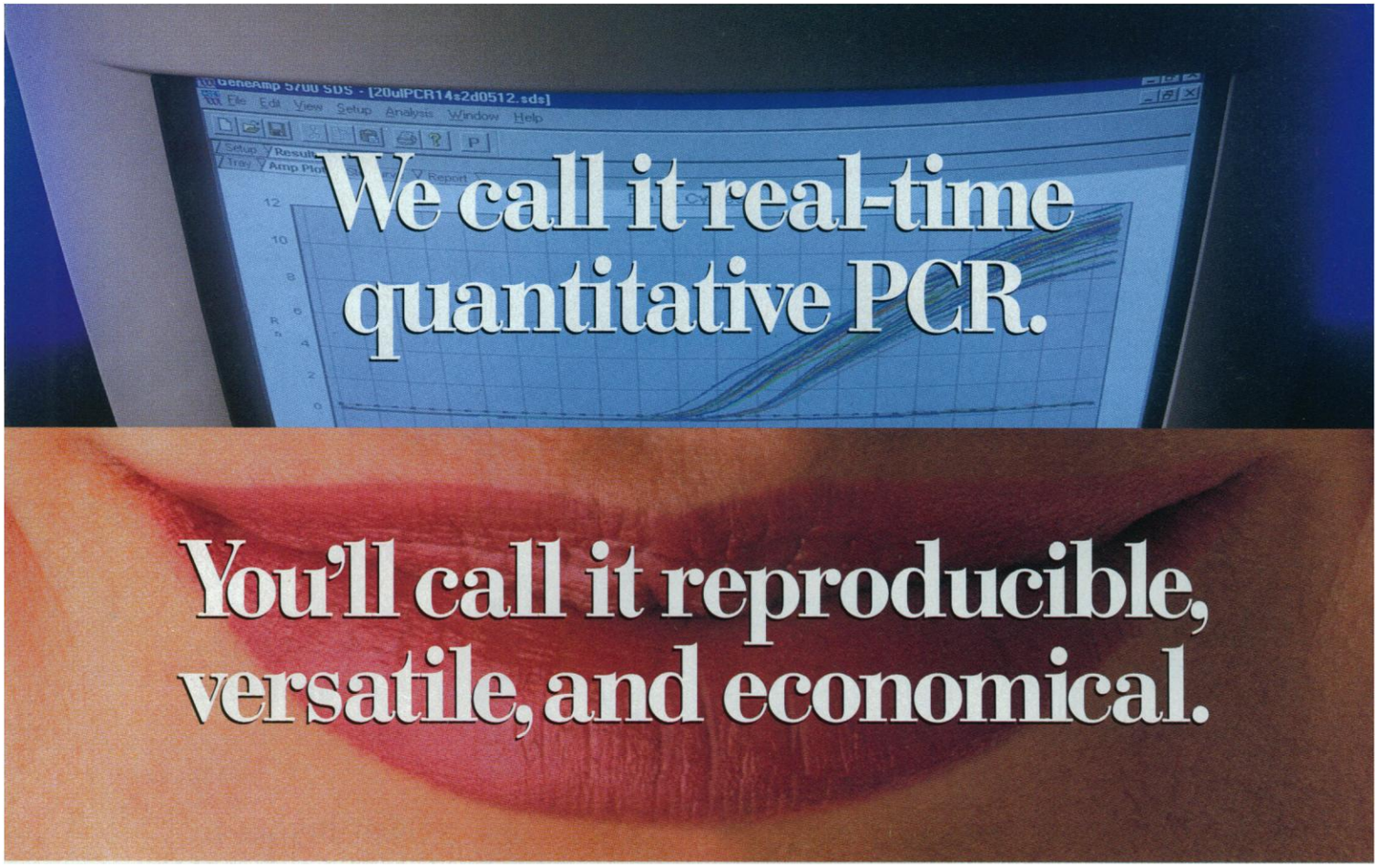

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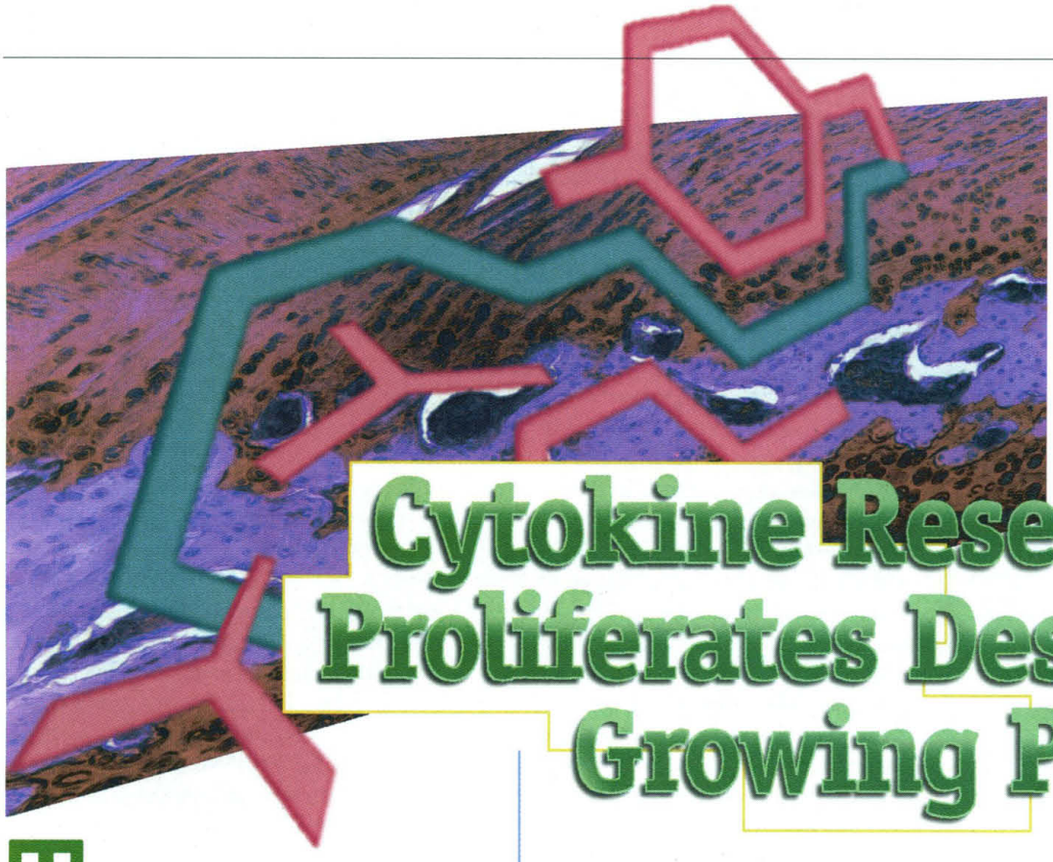

Cytokine Research Proliferates Despite Growing Pains

Products for cytokine research are expanding beyond that stalwart old workhorse, the sandwich assay. Recent market entries include assays for mRNA and new competitive assays. But the sandwich assay isn't ready to be put out to pasture yet. It's more versatile than ever, thanks to new detection methods, matched antibody pairs, and kits for animal cytokines.

The ancient maxim known as Occam's Razor, that the simplest explanation is the best, may have met its match in modern-day cytokine research. Even William of Occam would throw up his hands in despair at finding any simple way to organize or understand the cytokines, small messenger proteins whose number increase monthly, as do their known functions and interactions.

Chaos plagues even their terminology. Decades ago, peptides that acted against viruses were dubbed interferons. Similar peptides that influenced cell growth were discovered in various other disciplines and were named lymphokines and monokines, colony stimulating factors, and growth factors. Today, scientists recognize all these as sister members of a family of regulatory peptides that act over short distances. Yet what name this family should bear—cytokines? growth factors? something completely new?—is still up in the air.

The situation is somewhat better for the individual cytokines. Most have had multiple names because each discoverer of a function named the protein after that function. Yet, usually a single name gains favor once several proteins are discovered to have the same sequence and in fact be the same molecule. Helping to organize the cytokines further is that they can be sorted into families based on receptor use. Still, more than 150 cytokines have been cloned, with more being constantly discovered, so the Babel of multiple names is likely to continue.

The stunning complexity of cytokine biology has stimulated research on several levels, with manufacturers producing products for all these levels. At the most basic level, scientists discover new cytokines, sequence and clone them, and study their functions. Another level of research is using cytokines to explore the immune system and tease apart the interplay of the various cytokines. Here again, confusion reigns. Whether a particular cytokine stimulates or inhibits the growth of a particular cell type, for example, depends on what other cytokines are nearby and in what concentrations.

Clinical research is yet another level. Because cytokines play prominent roles in inflammation and many diseases, cytokines hold incredible promise as therapeutics and as therapeutic targets. But progress has been at turtle speeds. Most cytokines have so many functions that taming them to one task is a formidable challenge. Only a few cytokines with relatively narrow functions have passed through Food and Drug Administration approval processes and emerged as prescription drugs.

Cytokine Research

Supporting these various levels of research are dozens of companies providing hundreds of products. Popular products include recombinant versions of the cytokines and their receptors and antibodies to the cytokines and receptors. Another popular product has been kits for performing sandwich assays, so called because the sample protein ends up sandwiched between layers of antibodies. In this assay, one antibody captures the cytokine and holds it in place, and the second antibody, which is labeled, binds to the cytokine and serves as the basis for detection. The most popular sandwich assays are enzyme-linked immunosorbent assays (ELISAs), although newer assays, such as those using flow cytometry or based on amplification of the sample or its signal, are challenging their dominance.

This year witnessed some shakeups among major suppliers. In April, Becton Dickinson and Company (Franklin Lakes, NJ) signed an agreement to acquire PharMingen (San Diego) as a wholly owned subsidiary. In July, Genzyme General (Cambridge, MA) signed an agreement to sell its research products business to TECHNE Corp. (Minneapolis, MN), the parent company of R&D Systems.

The Challenge Of Keeping Abreast

"I'm continually impressed by how fast the fields [related to cytokines] are moving and how exciting the research is," says Robert Goldman, president of Peprotech Inc. in Rocky Hill, NJ, which manufactures recombinant proteins, including cytokines. Goldman singles out two families of cytokines his company finds particularly exciting: chemokines and the tumor necrosis factor (TNF)–related ligands.

"Chemokines are a whole group of relatively newly discovered small proteins that play a very important role in inflammation research, research into asthma, and more recently into HIV-related research," Goldman says. "In particular, chemokine receptors have been identified as important for the entry of the HIV virus into cells." These receptors must be present with another receptor called CD4 in order for HIV to bind to T-cells. "After that discovery, the interest in chemokines just exploded," Goldman says. Researchers are now trying to nail down how certain chemokine receptors allow HIV to breach the defenses of cells; pharmaceutical companies could then look for inhibitors that might fend off HIV infection.

Peprotech sells more than 30 human chemokines, including not only RANTES, Exodus-2 (also called 6Ckine), lymphotactin, and monocyte chemotactic proteins (MCPs) 1 through 4, but also eotaxin and fractalkine. Eotaxin has attracted the notice of researchers because it appears to play a powerful role in allergies and asthma. Fractalkine is particularly intriguing because it is structurally unlike the other chemokines. Unlike other cytokines, fractalkine and its receptors can act as adhesion molecules.

Usually, chemokines and other cytokines are similar enough from species to species that a researcher can use human cytokines in experiments with other animals, Goldman says. Still, some cytokines are species-specific, and some researchers prefer to use the actual cytokine for their animal model. So Peprotech sells many mouse and rat cytokines in addition to the corresponding human cytokines.

Another area of great interest in cytokine research right now for which Peprotech has developed a product line is the TNF-related ligands and their receptors. The grandparents of this family, TNF-α and TNF-β, were first isolated in 1985 after a long search for factors that could act against tumors. Since then, more than a dozen TNF-related ligand-receptor pairs have been discovered as well as various "orphan" ligands and receptors. The members of the TNF family have functions well beyond their first-discovered role as antitumor agents. Several members share a "death domain," an aptly named sequence that triggers apoptosis (programmed cell death). The TNF family also seems to take part in inflammation and regulating the immune system.

Peprotech is releasing several TNF-family members this year and plans to produce oth-

Cytokine Research

> "There are so many publications of new cytokines every week. Just keeping up with the science is another challenge."

ers as they are discovered. New products include CD27 ligand, CD30 ligand, CD40 ligand, TRAIL (also called Apo-2 ligand), RANK ligand (also called TRANCE), OX ligand, 4IBBL ligand, TWEAK, and LIGHT.

In addition to coming out with new cytokines and receptors as they are discovered, Peprotech has also focused on developing and releasing matched-pair antibody sets. Each set is a pair of antibodies to the same cytokine that have been tested to work well together in sandwich assays. One antibody is usually monoclonal and can be used as the capture antibody, and the other is polyclonal and can be used as the marker antibody. "Paired antibodies are essential for detecting the presence of cytokines in blood, serum, or culture media," Goldman says. For almost every cytokine, Peprotech has a corresponding polyclonal antibody. The company is now developing monoclonal antibodies to many of its cytokines, and "we are in the process of pairing monoclonal and polyclonal antibodies to check for compatibility for detection systems," Goldman says.

He pinpoints three challenges that face companies that manufacture cytokines. One is to make the most exciting of the newly discovered cytokines and receptors available to researchers as soon as possible. He says Peprotech can usually have a product ready 4 to 6 weeks after a cytokine's sequence has been published, but some difficult cytokines take longer. Goldman singles out these difficult cytokines, which may require special expression systems or some special technology to purify the active protein, as manufacturers' second challenge. And finally, he points to the sheer volume of new cytokines. "Research is going so quickly," he says. "There are so many publications of new cytokines every week. Just keeping up with the science is another challenge."

Building A Better Mousetrap

Improving on that mainstay of cytokine research, the ELISA sandwich assay, is a continual challenge for manufacturers in the cytokine field. One new approach to a better mousetrap is the CytoTrap Cytokine Stimulation Assay produced by BioSource International, Inc., of Camarillo, CA, which makes human, mouse, and rat cytokines and detection kits for cytokines and their genes. The CytoTrap is an ELISA that takes place entirely in a microwell and that has an unusual sample: cells.

"With most ELISA kits, you're measuring a supernatant from a cell line or serum sample or whole blood," says Valerie Bressler-Hill, BioSource's Director of Marketing. "In the CytoTrap, you add your sample with the cells in it directly to the assay and then stimulate the cell to produce the cytokine of interest."

"Where this is particularly interesting is in short-lived cytokines, such as IL-2 or IL-4," says Kevin Reagan, Vice President of Immunology. The CytoTrap assay measures the protein as soon as it's produced, so there's little time for it to be soaked up by soluble receptors or bound by other cells. In contrast, a regular ELISA run on serum for IL-4 generally detects nothing because IL-4 is so quickly absorbed.

The CytoTrap assay takes about the same length of time as a regular ELISA. Currently, CytoTrap assays are available for mouse IL-2 and mouse IL-4 (human kits are also available).

Despite the advantages of the CytoTrap in some situations, BioSource believes traditional ELISAs still fit the bill for many applications. In its CytoScreen line of solid-phase sandwich ELISAs, the company is expanding the range of animal models beyond the mouse. "Going after the major markers for rats has been an important strategy for the company," Reagan says. BioSource now has about a dozen CytoScreen kits for detecting rat interleukins, TNF-α, γ-interferon (IFN-γ), and chemokines. In addition, the company has several cytokine kits for monkeys and an IFN-γ kit for cattle, and it just recently released kits for pig TNF-α; IFN-γ; and interleukins 1β, 8, and 10.

"The swine is extremely important in the transplantation field because they are the most closely related model to humans," Reagan says. "In the transplantation area, there's a lot of cytokine work that's going on because the elicitation of certain cytokines predicts rejection."

Another recent BioSource product is the CytoXpress line of assays for quantifying cytokine mRNA (rather than the cytokine protein itself). Reagan says that measuring protein can present a problem. Assays may not pick up some protein, either because the amount is below the sensitivity of the assay or because the protein that's produced is not released or is bound immediately. By measuring mRNA, the CytoXpress assay reveals gene expression closer to the start of the process.

In the CytoXpress assay, the scientist converts the mRNA to cDNA and spikes the sample with a known quantity of a standard. Then the mixture is amplified by the polymerase chain reaction (PCR). The standard is designed so that the PCR primers bind both it and the sample. As a result, when the number of cDNA molecules at the start is between 20 and 20,000, the standard and sample amplify at the same rate.

After the PCR reaction, the standard and sample are measured. Because the starting number of copies of the standard is known and because the standard and the sample amplify with equal efficiency, the relative optical density of the two allows easy calculation of the number of cytokine cDNA molecules at the start.

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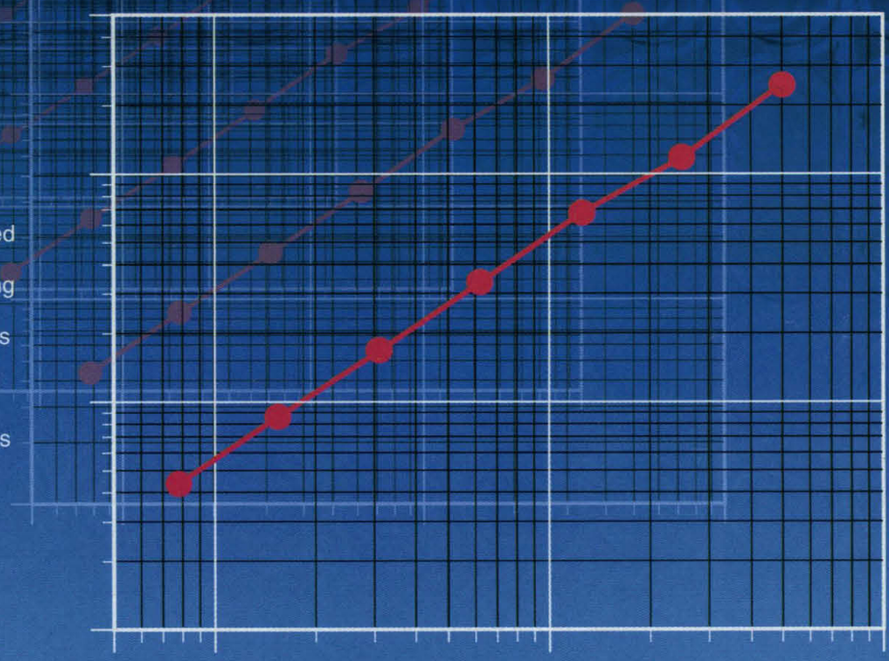

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IL-12 p40		IL-12 p70
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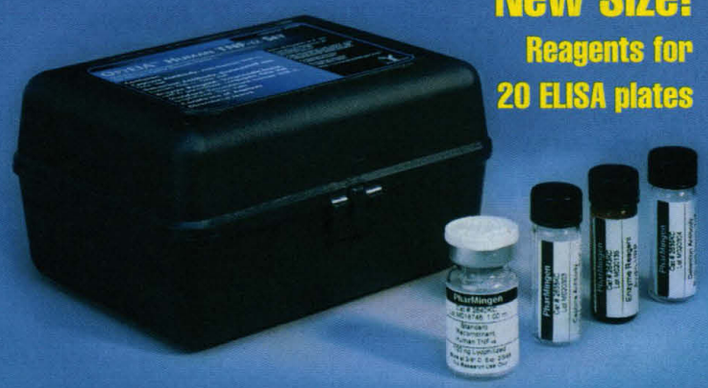

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Kits are available for measuring human and mouse IL-1β, -2, -4, -6, and 10; TNF-α; and IFN-γ. Rat kits are available for most of these as well.

For the future, Reagan and Bressler-Hill believe that current assay technologies just cannot be tweaked into doing everything that researchers need. Rather, companies will need to develop completely new technologies to overcome current limitations.

For example, the four hours it takes to run even the fastest current assays is painfully slow when researchers want to monitor minute-by-minute changes in cytokine concentrations. And current assays that measure only one or two cytokines at a time can't reveal the intricate dance of interactions between cytokines. Placing further demands on future assays, Reagan says, is that increases in speed and number of cytokines detected shouldn't come at the expense of sensitivity. Larger samples would then be needed, something that's just not practical for researchers working with tiny animals such as mice.

Cytokine Research

"In the transplantation area, there's a lot of cytokine work that's going on because the elicitation of certain cytokines predicts rejection."

On The Cytokine Frontier

Chemokines are generating great excitement right now at R&D Systems Inc. of Minneapolis, MN, a company that focuses on cell surface receptors and their ligands. "I can't overemphasize the amount of interest in chemokines and chemokine receptors," Thomas Detwiler, R&D's Vice President for Scientific Affairs, says. "We consider ourselves the dominant supplier of reagents in the chemokine field." In fact, R&D first came out with a line of chemokines, antibodies, and ELISA kits several years ago—and they bombed. "We were ahead of the curve," Detwiler says. Only after the discovery that chemokine receptors allow HIV to infect cells did the current explosion of interest in chemokine research—and the corresponding boom of sales of chemokine-related products—take place.

Currently, R&D sells about 330 chemokine-related products, including human, mouse, and rat chemokines; monoclonal and polyclonal antibodies (some biotinylated and some labeled directly with a fluorophore) to human, mouse, and rat chemokines; matched antibody pairs; and immunoassays for human and mouse chemokines. Of these products, about a quarter debuted in the past year.

Another research area that continues to flourish, Detwiler says, is the transforming growth factor–β (TGF-β) superfamily. TGF-β was first identified in 1981, and its name reflects its ability to prod certain normal cells to transform into cancerous ones. Its roles in cells have turned out to be startlingly broad, however, and TGF-β has turned out to be a member of an extensive family of proteins, including the activins, the inhibins, and the bone morphogenic proteins (BMPs). TGF-β and its superfamily are involved in nearly everything in the body.

R&D has recently started to expand its product line related to the TGF-β superfamily. Already out are polyclonal antibodies to human BMP-2; other activin, inhibin, and BMP products are in the works.

R&D's cytokine product line has been growing in other directions as well. In particular, the Quantikine sandwich ELISA kit line is branching into two new areas. One area is to supply a greater range of kits for mouse and rat cytokines. Among the new kits, called M Quantikine kits, are 21 kits for mice and two for rats.

The other branch is the Quantikine Ab kits for detecting autoantibodies to cytokines. "There is an increasing use of cytokines, especially hematopoietic growth factors, in therapeutic treatments," Detwiler says. "Some treated patients make antibodies against some of these, and some apparently healthy people who have never received therapeutic cytokines make autoantibodies against them." R&D Systems expects an increasing number of researchers to turn to studying the circumstances of development of these antibodies and their physiological consequences. The first two Quantikine Ab kits are for detecting antibodies to human IL-1α and human IL-6.

For situations in which Quantikine assays are not sensitive enough, require too much sample, or do not have enough dynamic range, R&D Systems recently introduced a new line of chemiluminescent sandwich immunoassays called QuantiGlo. "These assays are based on an enhanced luminol reaction with horseradish peroxidase," Detwiler says, which gives off light. "This gives you an inherently greater sensitivity and range than is possible with measurement of light absorbance." The emitted light is read with a luminometer. QuantiGlo standard curves typically span from less than 1 pg/mL to more than 2000 pg/mL, and the assay takes only four hours. Currently, QuantiGlo assays are available for six human cytokines—IL-1β, IL-4, IL-6, IL-12, TNF-α, and endothelin—with more assays under development.

"Diagnostic assays are being explored, but this [area] has been a disappointment to us and, I think, to many others as well," Detwiler says. "The relationships among cytokines are so complicated that claims for simple diagnostic applications are difficult."

Other future plans are clearer. R&D will continue to produce chemokines and their receptors as new ones are discovered and cloned, Detwiler says, and the company will expand its lines of reagents for apoptosis,

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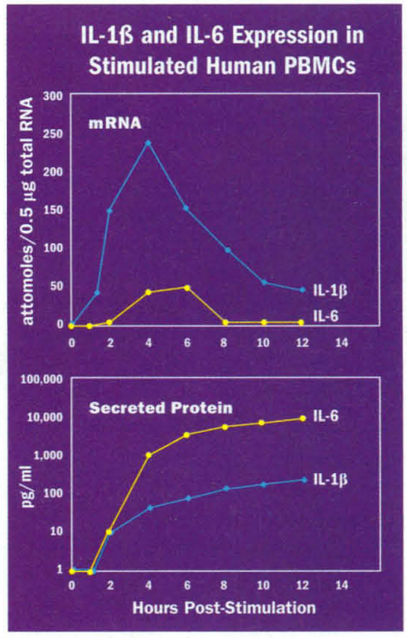

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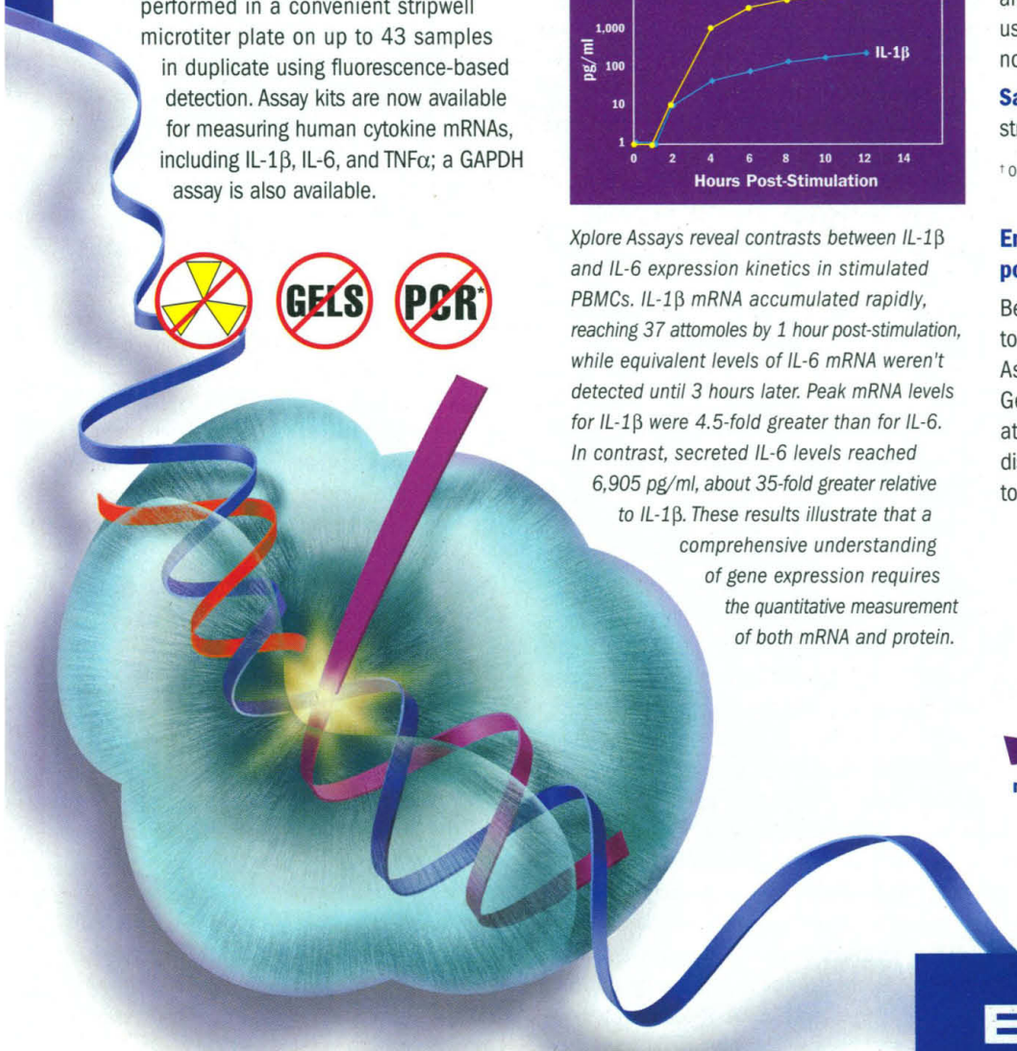

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Cytokine Research

> "Some apparently healthy people who have never received therapeutic cytokines make autoantibodies against them."

neurosciences, and developmental biology, areas in which it expects considerable growth. R&D is also beefing up its line of cytokine-specific molecular biology reagents with a new line of Quantikine mRNA kits that offer, Detwiler says, "a quick, simple alternative to Northern blots."

New Tools For New Problems

"Several aspects of gene expression haven't been explored in detail due to the lack of good tools," says Alan Kotik, Director of Marketing at Endogen, Inc., in Woburn, MA, a company that specializes in products for cytokine research. One example, Kotik says, is translational efficiency—that is, the number of cytokine molecules a cell can synthesize from a single transcript.

A new Endogen product, the Xplore assay, is designed to fill this slot—and several others—in the cytokine gene-expression research toolbox. Xplore assays directly quantify the number of mRNA transcripts for a specific cytokine in a 0.5-µg sample of total RNA.

In the assay, a researcher first hybridizes two probes to the target RNA. Because the probes' binding regions partially overlap, the "tail" of one probe, the signal probe, can't hybridize to the target and is clipped off by an enzyme called Cleavase VII. The number of these "signal probe fragments" generated is directly proportional to the original number of target mRNA molecules, resulting in precise signal amplification. Also, the assay is extremely sensitive because thousands of signal probe fragments can be generated for each molecule of target mRNA.

Next, the signal probe fragments are bound to a streptavidin-coated microtitration plate by means of a biotinylated capture oligonucleotide, and the fragments are detected by use of a fluorescent detection system. Comparing the fluorescent signal of the unknown sample with a standard curve allows precise quantification of the number of mRNA molecules in the sample. The assay takes about four hours and can detect as little as five attomoles of RNA. At least 40 samples can be run simultaneously.

"Because it's a signal amplification system, not a target amplification, you don't have issues with contamination," says Mark Moody, Endogen's Director of Molecular Biology. All Xplore assays are run under the same conditions, allowing the researcher to quantify many different cytokine mRNAs using the same assay procedure.

Currently, Xplore assays are available for human IL-1β, IL-6, and TNF-α messenger RNA as well as for the housekeeping genes β-actin and *GAPDH*. Over the next year, Endogen plans to introduce Xplore assays for a variety of human, mouse, and rat cytokines.

In addition, Kotik says, researchers studying expression of noncytokine genes "have expressed strong interest in the Xplore platform." Endogen is collaborating with these researchers to help them create custom probes that can be used in the Xplore assay system.

Customer needs have similarly driven other changes in Endogen product lines. Five years ago, immunoassay assay kits served most customers interested in measuring cytokine protein concentrations. But since then, researchers have increasingly needed to process larger numbers of samples for several cytokines. Some researchers have wanted to measure cytokines in unusual sample types. And some researchers have felt fettered by the fixed sensitivity, standard curve range, and detection system of prepackaged ELISA kits.

Endogen has responded to these needs in three ways. First, it has begun producing multipack versions of kits that are designed for processing large numbers of samples. Second, the company developed the "MiniKit," a reagent package that contains pretitered antibodies, calibrated cytokine standard, and instructions for rapidly setting up a cytokine ELISA. Third, Endogen has quadrupled its selection of matched antibody pairs. Matched antibody pairs allow researchers to construct customized assays from scratch, while bypassing any need to prequalify a large number of antibodies to ensure they will work well together.

"With the matched antibody pairs, researchers can develop cytokine assays with the sensitivity, dynamic range, and detection system of their choice," Kotik says.

For the future, Moody says, Endogen will continue to focus on developing advanced tools for studying gene expression. "Where people were looking at protein levels before, now they're looking at quantifying mRNA transcript levels too," Moody says.

Endogen is also expanding its range of tools for immunology research, particularly in rats and pigs. Both animals have become increasingly useful as models of human disease. The pig, for example, is now being used as a model for arteriosclerosis, asthma, and arthritis, in addition to being considered the prime source of organs for xenotransplantation.

Piecing Together The Puzzle Of Cytokine Interactions

"In our estimation, the most pressing problem in cytokine research and probably the most exciting to be unraveled over the next five years or so will be the clinical significance of cytokine changes in vivo," says Lawrence Tamarkin, President and CEO of CytImmune Sciences in College Park, MD.

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Tamarkin compares our current state of understanding of in vivo cytokine interactions to a jigsaw puzzle. "It's as if we have the puzzle with all the pieces in it, but we don't have the box top," he says. "We don't have a clear picture in vivo of what is actually going on, the relationship of one cytokine to another and how they respond to perturbations."

CytImmune's flagship product, the Accucyte assay, is designed to remedy this lack. The Accucyte assay measures cytokines directly in biological fluids. "It's become clear that the sandwich assay is a limited technology in that it does not appear to be going towards any clinical diagnostic potential," Tamarkin says. He cites in particular the problem that cytokines are quickly bound once they are released from cells, and they can become undetectable in traditional assays. Worse yet, the amount of binding varies from subject to subject and can be affected by sample handling. The result has been that measurements of cytokine proteins in seemingly similar populations have varied greatly from lab to lab.

The Accucyte assay is meant to measure cytokines at normal biological levels reproducibly and without being affected by the binding that stymies sandwich assays. Competitive hormone radioimmunoassays provided the inspiration for the assay design, which the company updated with some '90s' twists. In the old radioimmunoassays, the hormone was tagged with a radioisotope, and then the hormone competed for a limited number of antibody binding sites in a test tube. In the Accucyte assay, by contrast, CytImmune has bound polyclonal antibodies to a microtitration plate well. The researcher adds a biotinylated standard containing a known amount of the cytokine and at least 50 µL of sample. Because polyclonal antibodies offer a variety of binding sites, even protein-bound sample can bind to them.

In fact, the standard, the protein-bound sample, and the free sample all have equal chances of binding to the limited number of polyclonal antibodies. Because the amount of the standard is known, the amount of cytokine in the sample can be easily computed. The Accucyte assay takes about four hours to run and can detect minuscule (0.20 to 200 ng/mL) amounts of cytokines in blood or other body fluids.

"We hope that the Accucyte will be used as a biological response marker to look at the changes in these very powerful hormones as they respond to immunological changes," Tamarkin says.

Tamarkin says that the primary customers for the Accucyte assay are scientists moving from in vitro to in vivo studies of cytokine regulation. "The basic scientists who are trying to look at mechanisms of action and in vitro regulation are well served by the sandwich assay," says Tamarkin, whose company also sells traditional ELISAs for human and mouse cytokines and polyclonal antibodies to human and rodent cytokines. "It's quantitatively accurate, it's precise, and it's sensitive." It's just not, in his view, useful for biological fluids.

The newest Accucyte kit measures endostatin, a cytokine that blocks the growth of blood vessels and so starves tumors of nourishment. CytImmune already had Accucyte kits for two cytokines that encourage the growth of blood vessels, vascular endothelial growth factor (VEGF), and fibroblast growth factor basic (bFGF). "In a fairly broad spectrum of current scientific endeavors, these factors play a critical role in understanding recovery and response and maintaining of health," Tamarkin says. The angiogenic and antiangiogenic factors may play a role not just in cancer but also in autoimmune disease, cardiovascular disease, ulcer healing, and rejection of transplanted organs. Tamarkin says these three kits together allow a scientist to explore how these cytokines relate and how the balance among them gets thrown off in disease.

Besides the kits for endostatin, VEGF, and bFGF, CytImmune also sells Accucyte kits assays for human IL-1α, -1β, -2, -3, -4, -6, -7, -8, -10, -13, and -15; epidermal growth factor; IFN-α; leptin; MIP-1α; RANTES; TNF-α; and TNF-β as well as six kits to measure mouse cytokines.

Because new cytokines and new functions of existing cytokines are constantly being discovered, companies' plans for the future are necessarily hazy. Who knows what lies around the next bend? Still, it seems clear that both improving the sandwich assay and developing alternatives to it will be high on many companies' lists of priorities.

The many advantages that have boosted the sandwich assay into its current central position in cytokine research likely will keep it there some time yet. But the assay's limitations are chafing more and more. Scientists are eager to have assays that are faster, that can measure several cytokines at once, that aren't confounded by protein-bound cytokines, and that work with unusual sample types, and companies will be eager to oblige.

—Shauna S. Roberts

Shauna S. Roberts is a science and medical writer in New Orleans.

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Conference Title	Chair	Date	Location
Angiotensin	Tomas Unger	Aug. 8-13	Queen's College, Oxford
Antimicrobial Peptides	Julyes A. Hoffman / Willem Broekaert	April 25-30	Il Ciocco, Italy
Barrier Function of Mammalian Skin	Hans Schaefer	April 18-23	Il Ciocco, Italy
Catecholamines	Marie F. Chesselet	July 25-30	Queen's College, Oxford
Cement-Based Materials, Chemistry & Physics of	Thomas Mason / Luigi Cassar	May 9-14	Il Ciocco, Italy
Chronobiology	Eberhard Gwinner	June 13-18	Il Ciocco, Italy
CO2 Fixation & Metabolism in Green Plants	Hans J. Bohnert	Sept. 12-17	Queen's College, Oxford
Computational Aspects of Biomolecular NMR	Jeffrey C. Hoch	June 6-11	Il Ciocco, Italy
Energetic Materials	Peter J. Haskins	July 18-23	Queen's College, Oxford
Floral Scent, Biology and Chemistry of	L. Gunnar Bergstrom	Sept. 5-10	Queen's College, Oxford
Genetic Toxicology	Leona D. Samson	Aug. 1-6	Queen's College, Oxford
Green Chemistry	James Clark / Roger Sheldon	July 11-16	Queen's College, Oxford
Immunochemistry & Immunobiology	Dan Littman	May 30-June 4	Il Ciocco, Italy
Laser Diagnostics in Combustion	Katharina Kohse-Höinghaus	June 20-25	Il Ciocco, Italy
Mechanisms of Cell Signaling	Louis Lim	Sept. 5-10	Singapore
Modern Developments in Thermodynamics	Bjarne Andresen	April 18-23	Il Ciocco, Italy
Molecular Evolution	Andrew Clark / Naoyuki Takahata	Oct 24-29	Japan
Neuroethology: Behavior, Evolution, and Neurobiology	John Hildebrand	Aug. 29-Sept. 3	Queen's College, Oxford
Oscillations & Dynamic Instabilities in Chemical Systems	Raima Larter	June 6-11	Il Ciocco, Italy
Polyamines	Philip Coffino / Kazuei Igarashi	Aug. 22-27	Queen's College, Oxford
Polymers (East)	Gerhard Wegner	July 4-9	Queen's College, Oxford
Solid State Chemistry II (Europe)	Gerard Ferey	Sept. 19-24	Queen's College, Oxford
Staphylococcal Diseases	Keith Dyke	May 9-14	Il Ciocco, Italy
Viruses & Cells	Patricia Spear	May 2-7	Il Ciocco, Italy

1999 SUMMER — NEW HAMPSHIRE / RHODE ISLAND / CONNECTICUT

Conference Title	Chair	Date	Location
Analytical Chemistry	J. Michael Ramsey	Aug. 1-6	New England College
Angiogenesis and Microcirculation	Patricia D'amore	Aug. 15-20	Salve Regina University
Applied & Environmental Microbiology	Lily Y. Young	July 3-8	Connecticut College
Archaea: Ecology, Metabolism & Molecular Biology	Steve Zinder / Felicitas Pfeifer	Aug. 1-6	Proctor Academy
Atherosclerosis	Jay W. Heinecke / Goran K. Hansson	June 20-25	Kimball Union Academy
Atmospheric Chemistry	William H. Brune / Joyce E. Penner	June 13-18	Salve Regina University
Atomic Physics	John Delos	July 4-9	Plymouth State College
Barriers of the Central Nervous System	Joanna Szmydynger-Chodobska / Adam Chodobski	Aug. 15-20	Tilton School
Bioenergetics	William Allison	June 27-July 2	Proctor Academy
Biological Structure & Gene Expression	Stephen Farmer	Aug. 15-20	Kimball Union Academy
Biomaterials: Biocompatibility/Tissue Engineering	Peter C. Johnson	July 18-23	Holderness School
Bioorganic Chemistry	Steven Rokita / Thomas Von Geldern	June 13-18	Proctor Academy
Bones & Teeth	Gordon J. Strewler	July 4-9	Kimball Union Academy
Calcium Signalling	Andrew Thomas	Aug. 8-13	New England College
Cancer	Tyler Jacks	Aug. 1-6	Salve Regina University
Carbohydrates	Jacques Van Boom	June 20-25	Tilton School
Catalysis	W. Curtis Connor	June 20-25	Colby-Sawyer College
Cell Contact & Adhesion	Barry Gumbiner	June 6-11	Proctor Academy
Cell Death	Douglas R. Green	June 27-July 2	Colby-Sawyer College
Cell Proliferation, Molecular & Genetic Basis of	Helen Piwnica-Worms	July 4-9	Colby-Sawyer College
Cellulases & Cellulosomes	David B. Wilson / Edward A. Bayer	July 25-30	Proctor Academy
Ceramics, Solid State Studies in	Dawn Bonnell / W. Craig Carter	Aug. 1-6	Kimball Union Academy
Chemical Oceanography	Bjorn Sundby	Aug. 8-13	Kimball Union Academy
Chemotherapy Of Experimental & Clinical Cancer	Neil Gibson	July 11-16	Colby-Sawyer College
Clusters, Nanocrystals & Nanostructures	Jim Heath	July 24-29	Connecticut College
Coastal Ocean Modeling	Christopher N. K. Mooers	June 20-25	Colby-Sawyer College
Coatings & Films	Robert F. Brady, Jr.	July 11-16	Colby-Sawyer College
Collagen	Gerhard Karsenty	July 25-30	Colby-Sawyer College
Combinatorial Chemistry	Anthony W. Czarnik / Herve Bouchard	July 4-9	Tilton School
Comparative Hematopoiesis	Jerry J. Kaneko / Milton J. Becker	Aug. 8-13	Tilton School
Condensed Matter Physics	David Grier	June 12-17	Connecticut College
Corrosion - Dry	Michael Schutze	July 18-23	Colby-Sawyer College
Developmental Biology	Liz Robertson / Barbara Meyer	June 20-25	Proctor Academy
Drug Metabolism	Steve Wrighton	July 4-9	Holderness School

Conference Title	Chair	Date	Location
Dynamics At Surfaces	Aart W. Kleyn	Aug. 8-13	Proctor Academy
Dynamics of Simple Systems in Chemistry & Physics	Colston Chandler	July 11-16	Salve Regina University
Elastin & Elastic Fibers	Francesco Ramirez	July 18-23	Kimball Union Academy
Elastomers	C. Michael Roland	July 18-23	Colby-Sawyer College
Electronic Materials: Chemistry/Excitations/Processes	Will Rees / Horia Metiu	July 4-9	New England College
Enzymes, Co-enzymes & Metabolic Pathways	Dan Herschlag / Charles Grissom	July 11-16	Kimball Union Academy
Epigenetics	Amar Klar / Jean Finnegan	Aug. 8-13	Holderness School
Epithelial Differentiation & Keratinization	Fiona M. Watt	July 18-23	Tilton School
Excitatory Amino Acids & Brain Function	Darrell W. Brann	June 27-July 2	Plymouth State College
Fertilization & Activation of Development	Diana Myles	July 25-30	Holderness School
Fiber Science	Peter Schwartz	July 4-9	Colby-Sawyer College
Forested Catchments: Hydrological/Geological/Biological Processes of	Sherry Schiff / Nico Van Breemen	July 18-23	Proctor Academy
Free Radical Reactions	Dennis P. Curran	July 11-16	Holderness School
Fuel Cells	Mordecai Shelef / Shimshon Gottesfeld	June 27-July 2	Plymouth State College
Gravitational Effects In Physico-Chemical Systems	Robert F. Sekerka	June 27-July 2	New England College
Heterocyclic Compounds	Joe Konopelski	June 27-July 2	Salve Regina University
Hormonal Carcinogenesis	Shuk-Mei Ho	Aug. 1-6	Tilton School
Hormone Action	Holly Ingraham	July 25-30	Kimball Union Academy
Human Molecular Genetics	Uta Francke	Aug. 8-13	Salve Regina University
Hydrogen-Metal Systems	Arnulf J. Maeland / Michele Gupta	July 18-23	New England College
Illicit Substance Detection	Ray Mintz	Aug. 8-13	Salve Regina University
Innovations in College Chemistry Teaching	Barbara Sawrey	June 19-24	Connecticut College
Inorganic Chemistry	Kim Dunbar	July 18-23	Salve Regina University
Ion-Containing Polymers	Robert Prud'homme / William Risen	June 20-25	Salve Regina University
Lipids and Lipid Mediators	William Dowhan	June 27-July 2	Kimball Union Academy
Liquid Crystals	David Walba	June 6-11	Tilton School
Liquids, Chemistry & Physics of	Michael Klein	Aug. 1-6	Holderness School
Magnetic Resonance	Regitze R. Vold	June 27-July 2	New England College
Mammary Gland Biology	Margaret Neville	June 6-11	New England College
Materials Processes far from Equilibrium	Tomas Diaz de la Rubia	July 11-16	Plymouth State College
Matrix Isolated Species, Physics & Chemistry of	Bruce Ault	July 11-16	Plymouth State College
Matrix Metalloproteinases	Gillian Murphy	Aug. 8-13	Colby-Sawyer College
Mechanisms of Membrane Transport Proteins	Jack H. Kaplan	June 20-25	Holderness School
Medicinal Chemistry	William Michne	Aug. 1-6	Colby-Sawyer College
Metamorphosis	Lynn M. Riddiford / Peter Cherbas	July 10-15	Connecticut College
Microbial Population Biology	Howard Ochman	July 18-23	Plymouth State College
Molecular Cell Biology	Elaine Fuchs	June 13-18	Tilton School
Molecular Mechanisms of Microbial Adhesion	Scott Hultgren / Guy Cornelis	Aug. 1-6	Salve Regina University
Molecular Membrane Biology	Tom Rapoport	July 4-9	Proctor Academy
Molten Salts & Liquid Metals	David Price	July 25-30	New England College
Molybdenum & Tungsten Enzymes	Edward Stiefel / Russ Hille	July 4-9	Plymouth State College
Muscle: Contractile Proteins	Sarah Hitchcock-DeGregori	June 6-11	Colby-Sawyer College
Mycotoxins & Phycotoxins	John Ramsdell / Mark Poli	June 20-25	Plymouth State College
Natural Products	George F. Majetich	July 25-30	New England College
Neural Plasticity	Larry Katz	July 18-23	Salve Regina University
Neurotrophins	Louis Reichardt	June 6-11	Salve Regina University
Neurovirology	Kamel Khalili	June 6-11	Colby-Sawyer College
Non-Antibiotic Properties of Tetracyclines	Robert Greenwald	July 11-16	Proctor Academy
Nonlinear Optics and Lasers	Andrew Weiner	July 25-30	Colby-Sawyer College
Nuclear Chemistry	I. Yang Lee	June 13-18	Colby-Sawyer College
Nuclear Physics	Xiangdong Ji	July 25-30	Salve Regina University
Nucleic Acids	Jim Maher / James R. Williamson	July 4-9	Salve Regina University
Organic Photochemistry	Ian R. Gould	July 17-22	Connecticut College
Organic Reactions & Processes	Terry Rathman	July 11-16	New England College
Organic Thin Films	Mary Galvin	July 11-16	Salve Regina University
Organometallic Chemistry	Gary S. Silverman / Richard Fisher	July 25-30	Salve Regina University
Origins of Solar Systems	Alan Boss	June 13-18	New England College
Parasitism	John Boothroyd	June 20-25	Salve Regina University
Phagocytes	R. Alan Ezekowitz	June 6-11	Connecticut College
Photoacoustic & Photothermal Phenomena	Joan Power	June 27-July 2	Colby-Sawyer College
Photoions, Photoionization & Photodetachment	Erwin Poliakoff	July 18-23	Plymouth State College
Photosynthesis	John Golbeck	June 13-18	New England College
Physical Organic Chemistry	Maitland Jones, Jr	June 27-July 2	Holderness School
Plant Cell Genetics & Development	Michael L. Christianson	June 6-11	New England College
Plasmid & Chromosome Dynamics	Dhruba Chattoraj	Aug. 1-6	Colby-Sawyer College
Polymer Colloids	Francoise M. Candau	June 27-July 2	Tilton School
Proteins	Susan Marqusee	June 13-18	Holderness School
Purines, Pyrimidines & Related Substances	Vasu Nair	July 4-9	Salve Regina University
Quantitative Structure Activity Relationships	Gerald Maggiora	July 25-30	Tilton School
Quantum Control of Atomic & Molecular Motion	Robert J. Gordon / Paul Brumer	Aug. 1-6	Plymouth State College
Quinone & Redox Active Amino Acid Co-Factors	Joanne Stubbe	June 13-18	Kimball Union Academy
Reactive Polymers, Ion Exchangers & Adsorbents	Steven M. Cramer	July 18-23	New England College
Red Cells	Phillip Low	July 11-16	Tilton School
Rock Deformation	Brian Evans	Aug. 8-13	Colby-Sawyer College
Second Messengers & Protein Phosphorylation	Jeremy W. Thorner	June 6-11	Kimball Union Academy
Statistics In Chemistry & Chemical Engineering	Anthony C. Atkinson	July 25-30	Plymouth State College
Supramolecules & Assemblies, Chemistry of	Eric Kaler / Thomas L. Penner	Aug. 1-6	New England College
Thin Films & Crystal Growth Mechanisms	Leo J. Schowalter / Jim J. DeYoreo	June 20-25	Plymouth State College
Three Dimensional Electron Microscopy	Bridget Carragher	June 20-25	New England College
Undergraduate Microbiology Education	Jeffrey J. Sich / Robin Patterson	June 26-July 1	Connecticut College
Wound Repair	Frederick Grinnell	June 13-18	Colby-Sawyer College
X-Ray Physics	Sunil Sinha	July 25-30	Plymouth State College
Zeolitic & Layered Materials	Prabir Dutta	June 13-18	Plymouth State College

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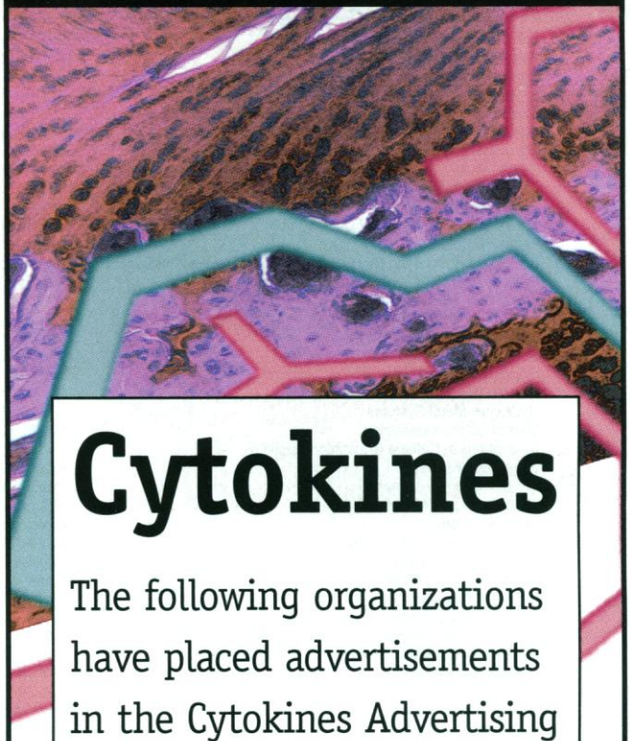

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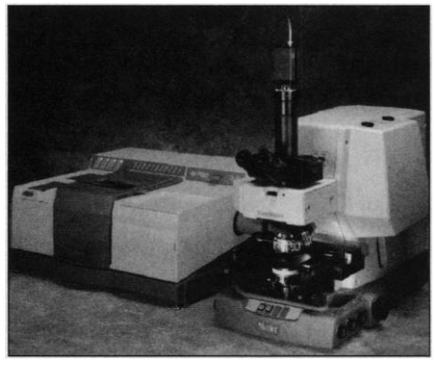

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