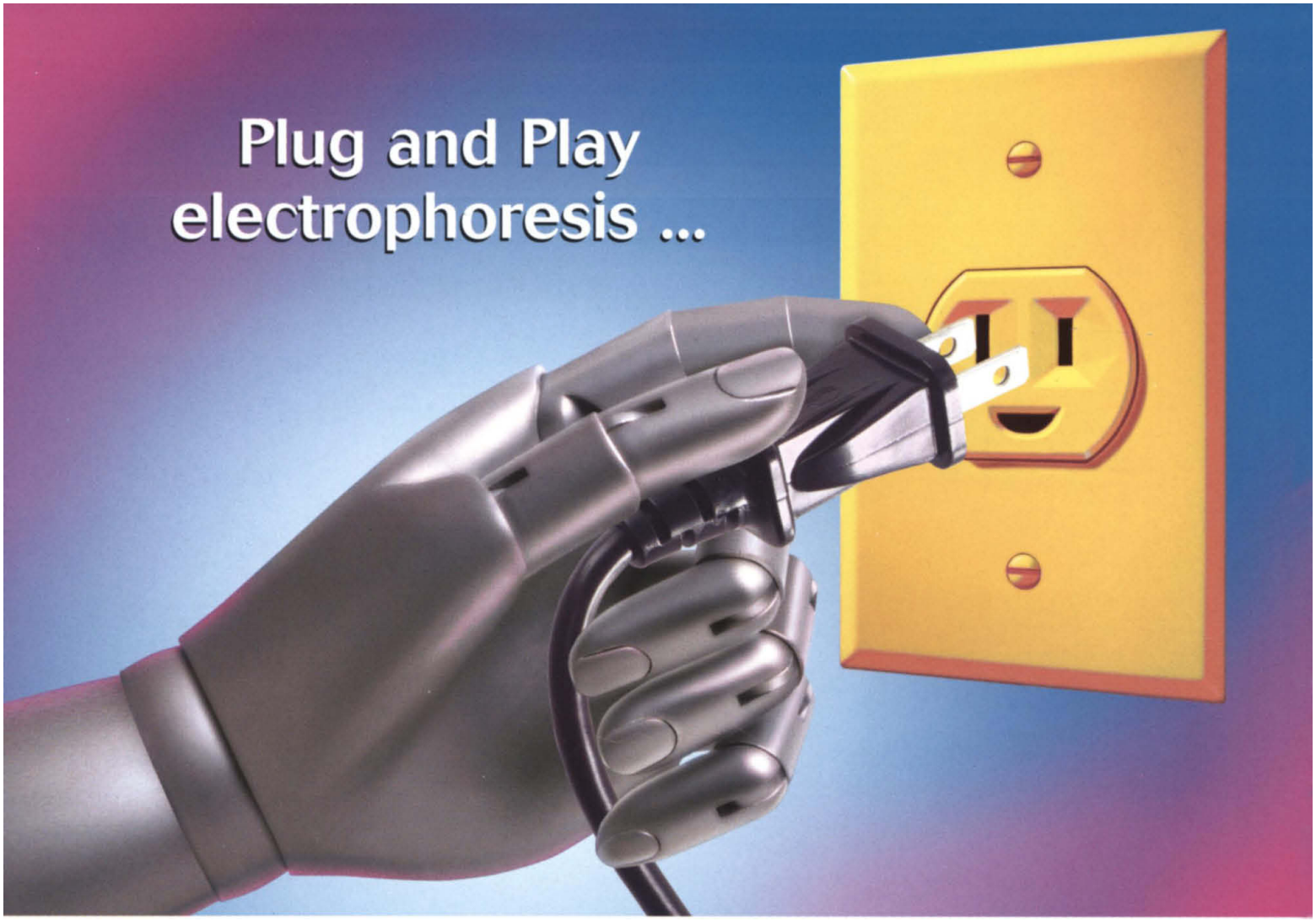

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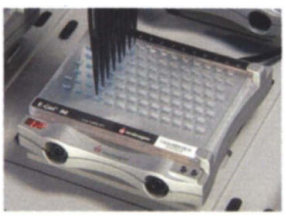

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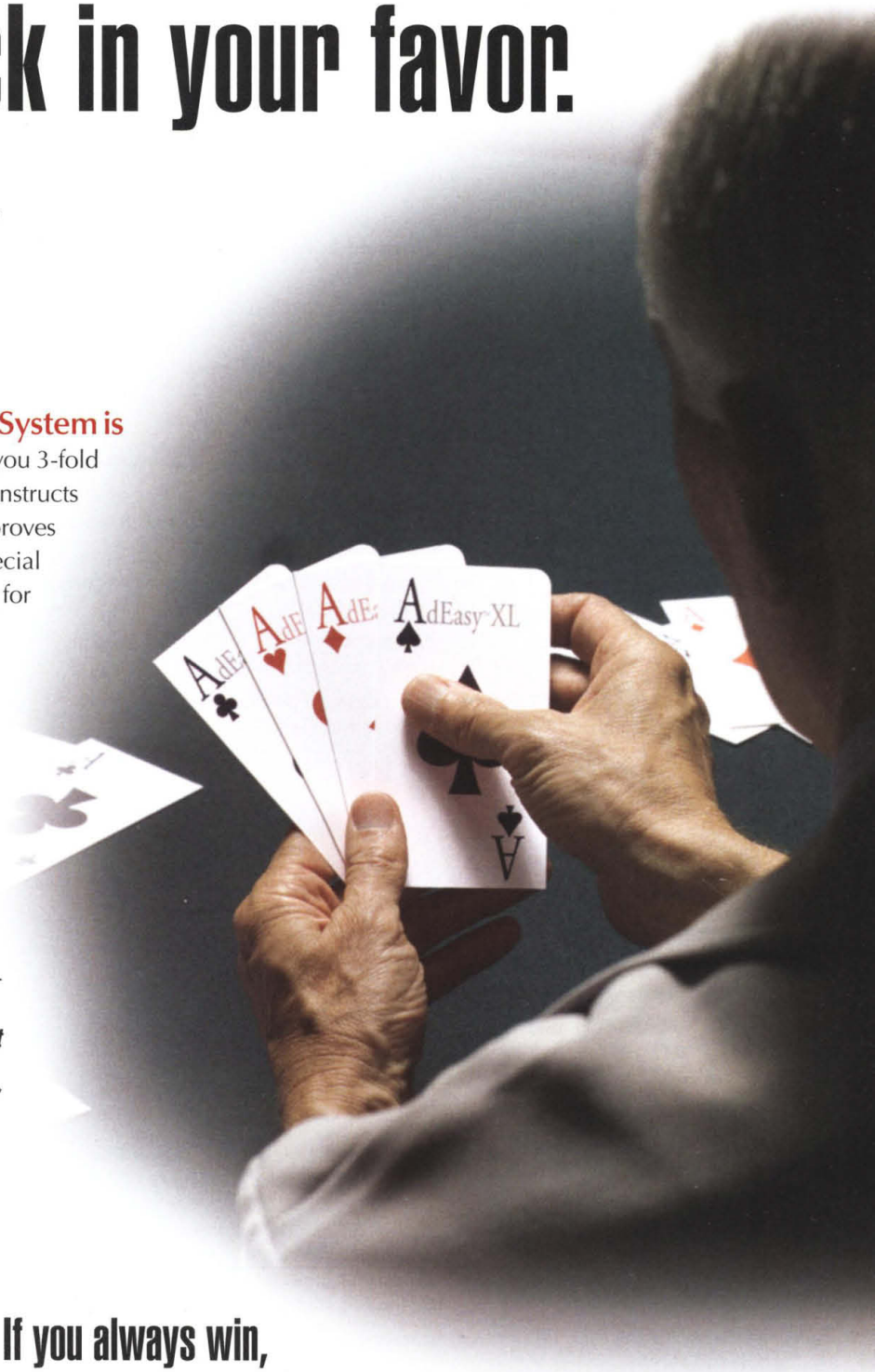

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Science

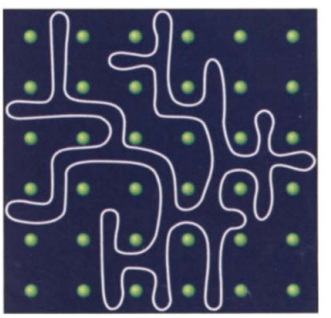
Volume 297 20 September 2002 Number 5589

NEWS

1988
Tracking West Nile

SCIENCE'S COMPASS

2002
Plant development and miRNA



2005
Polymers with a difference

RESEARCH

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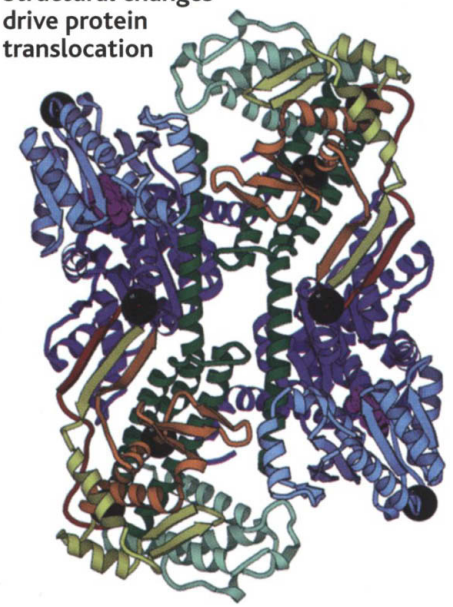
RESEARCH ARTICLES

2018

Structural changes drive protein translocation



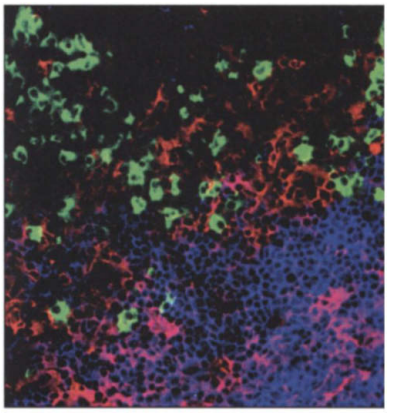
REPORTS

COVER 2030

A proposed structure of the He_8–carbonyl sulfide (OCS) supermolecule, as construed from vibrational and rotational spectroscopic data. The formation of the first helium solvation layer begins with an equatorial "doughnut" of five helium atoms around the OCS molecule. The spectroscopic study of successive solvation of OCS with helium atoms may shed light on the origins of superfluidity. [Image: W. Jäger and K. Brendel]

2066

Mutating B cells relocate



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CONTENT HIGHLIGHTS AS OF 20 SEPTEMBER 2002

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SCIENCE EXPRESS

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Direct Observation of Percolation in a Manganite Thin Film L. Zhang, C. Israel, A. Biswas, R. L. Greene, A. de Lozanne

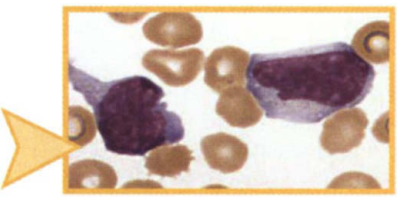
Scanning probe microscopy is used to directly image percolation networks evolving in manganite thin films.

Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes M. E. Dudley *et al.*

1973 Transfer of reactive T cells leads to tumor shrinkage in patients with melanoma.

Structural Basis for the Transition from Initiation to Elongation Transcription in T7 RNA Polymerase Y. W. Yin and T. A. Steitz

The 2.1 Å resolution structure of a T7 RNA polymerase elongation complex reveals dramatic conformational changes that explain the processivity of transcription in the elongation phase.



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NETHERLANDS: Nanotechnology—The Talk of the Scientific Town D. N. Reinhoudt and J. Huskens

Global trends in nanotech precipitate exciting opportunities for young researchers.

CANADA: "Thank you, India" M. Wightman and N. Robitaille

Canadian sociologist Brenda Cranney is grateful for a research experience that changed her life.

US: EmPOWREment and ADVANCEment—NSF Programs for Women in Science M. Kempf

The NSF shifts its gender equity focus toward institutional initiatives.

SINGAPORE: From the Crime Scene to the Trial J. Wong

There's no typical day for scientists in the Criminalistics Laboratory at Singapore's Centre for Forensic Science.

UK: Yours Transferredly—The Approaching Ph.D. Viva P. H. Dee

Do you feel upbeat and confident about your viva, or are you simply hoping to survive it?

GLOBAL: Science in the Developing World—Building Partnerships for the Future J. Coloma and E. Harris

The authors founded an organization that specializes in technology transfer to Latin America.

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PERSPECTIVE: Mitigating the Tithonus Error—Genetic Analysis of Mortality Phenotypes S. D. Pletcher

Measuring maximum life-span is not sufficient.

NOTEWORTHY THIS WEEK: Nuclear Fallout M. Beckman

Mice lacking a nucleus-bracing protein appear to age quickly.

NOTEWORTHY THIS WEEK: BRCA Breakthrough M. Leslie

Scientists uncover the job of a breast cancer protein.

NOTEWORTHY THIS WEEK: A Fix on AlkB R. J. Davenport

A DNA-repair protein removes methyl groups through an unprecedented mechanism.

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signal transduction knowledge environment

PERSPECTIVE: At the Crossroads of Necrosis and Apoptosis—Signaling to Multiple Cellular Targets by HM GB1 M. Bustin

How a nuclear protein may be a key determinant of cell death pathways.

PERSPECTIVE: Id—A Target of BMP Signaling K. Miyazono and K. Miyazawa

Dominant-negative inhibitor of basic helix-loop-helix transcription factors functions in signaling by TGF-β family members.

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THE MJ RESEARCH NOTEBOOK

Volume XII...No. 1 *A Bulletin of Technological Advance in Molecular Biology* *Fall 2002*

Use SYBR® Green or Probe Methods? It's Up to You

Almost All Chemistries Work Well

A wide variety of methods are now available for the quantification of RNA or DNA signals—and virtually all of them can work well in the DNA Engine Opticon™ system.

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For many investigators, reactions using SYBR green dye are proving to be particularly propitious. Recent data have shown high specificity and broad applications for such assays *(Morrison, TB et al* BioTechniques *(24) 954-960).* These tests are easy to design and quick to execute, requiring only one pair of well optimized primers—along with SYBR Green I reagent. After amplification, melt curves can verify the ID of the product, and Opticon's handy full-width, half-max function can indicate purity as well.

However, many scientists prefer probe-based assays, like TaqMan®, molecular beacons, or newer, minor-grove-binding systems. Every method tested thus far works well in an Opticon system, provided the assay can incorporate a dye that can excite at 450-495nm and be read at 530nm±15 (like fluorescein, FAM, SYBR, etc.)

Bear in mind that Opticon is a one-color system—but this allows for simplicity and extraordinary performance at a low price (and a two-color upgrade will be forthcoming soon).

Troubleshooting with a Gradient

The Opticon system brings with it the many features of the refined DNA Engine™ cycler on which it is based. Among these is a thermal gradient function that helps optimize protocols and troubleshoot problematic reactions.

This feature allows temperatures to be systematically varied 1°-24°C across the block—for precise tuning of annealing, reading, or denaturing temps. This is especially helpful with real-time protocols, for getting the lowest cycle threshold (C_t) often involves empirical optimization specific to the detection chemistry used.

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From the beginning, Opticon systems were designed to perform melt curves. Stepped denaturations are monitored for the nuances of the dissociation of DNA as temperature rises. These data can verify IDs of multiple amplification products within each tube, as well as indicate purity through a half-max analysis.

SYBR green is typically used as the reporter. It fluoresces intensely as it binds dsDNA, but as the complex melts, its signal fades by orders of magnitude as the dye comes to float freely among single strands. Thus the unit can serve as a 96-well melt-curve analyzer—as well as a regular fluorescence plate reader at 530nm±15.

Affordable & Versatile—w/Format Convenience

Real-time cyclers have been around for a few years—but most designs have been extraordinarily expensive, or limited in function, or required the use of odd vessel formats.

Due to the simplicity of its patent-pending design, the DNA Engine Opticon system delivers performance second to none—at a price few can match. Current owners of PTC-200 cyclers can save money by having their existing instrument upgraded (US & Canada only).

For the scientist at the bench—the 96-well format may be paramount. It is easily loaded, easily analyzed, and it facilitates high throughput. For those watching the bottom line—the unit's sensitivity allows very economical operation. Volumes of 20µl can be used routinely; in many hands, 10µl reactions work as well.

"SYBR" is a registered trademark belonging to Molecular Probes, Inc.

UNIQUE DETECTION TECHNOLOGY

Blue LEDs Excite, PMT Detects

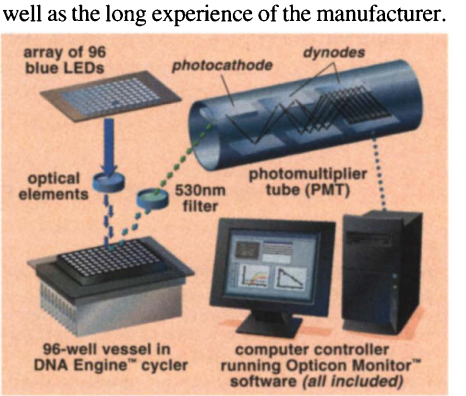
WALTHAM, Mass. — MJ RESEARCH, INC. announces the introduction of a wholly new type of real-time thermal cycler capable of performing a variety of biochemical functions.

What makes this instrument unique is its method for fluorescence excitation and detection. Rather than rely upon a CCD camera or optical fibers—the instrument incorporates a simple but elegant approach that addresses each well individually with an array of blue LEDs and a PMT (see below). The result is not only great sensitivity—but as well reproducibility in quantification as rare as a blue diamond.

Specifically, an individual blue LED fires a pulse of light, which travels through optics to excite a single well in a 96-well plate. Reaction-dependent dyes in the sample fluoresce, flashing a signal to a photomultiplier tube through an optical filter. The PMT progressively amplifies the signal through 11 stages—quantitating even the weakest signal precisely.

All 96 wells in a plate can be sampled in less than 3 seconds. Since the wells are flashed individually in sequence—problems of cross-talk are minimized. Furthermore, strong signals adjacent to weak/negative signals are no problem—unlike with camera-based systems.

Lastly, the system is built around MJ's well-proven DNA Engine cycler, thus users can rest assured of the precision of thermal control, as well as the long experience of the manufacturer.



Excitation, detection & quantification

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

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THIS WEEK IN Science

edited by Phil Szuromi

Laser Key to Cryptography

Modern encryption of messages relies on "one-way" functions that are easy to compute in one direction but difficult to deconvolute in the other. Pappu *et al.* (p. 2026) present a physical one-way function based on the pattern generated by scattered laser light through a disordered medium. The resultant speckle pattern can be processed into a numeric key of fixed length and may be useful as a secure identification and information-encoding technology.

2030 Strength in Smaller Numbers

At what point do helium atoms in cryogenic clusters show superfluidity effects? Tang *et al.* (p. 2030; see the cover) obtained high-resolution spectra of the rotational and vibrational motion of OCS molecules in clusters containing two to eight helium atoms. The helium atoms appear to form an equatorial "donut" around the molecule, and the rotational constant falls below the bulk droplet limit for six to eight helium atoms. These results suggest that in smaller clusters, before the onset of superfluidity, the helium atoms in the closest shell are more tightly bound than in bulk clusters, where they can undergo long-path exchange with other helium atoms and thus decrease their binding strength.

Running Rings into Polymers

The synthesis of high-molecular-weight cyclic polymers is often inefficient because the final intramolecular ring closure step demands dilute conditions and is often hampered by chain entanglement. Bielawski *et al.* (p. 2041; see the Perspective by McLeish) have synthesized cyclic polyethylene molecules with molecular weights up to 200 kilodaltons through a ring-opening metathesis polymerization that tethers the growing chain until it is eliminated as a cyclic species. The cyclic polyethylenes differ from their linear isomers in physical properties such as viscosity.

Everyday Wear and Tear

It is generally assumed that huge floods play a disproportionate role in modifying river courses and eroding bedrock. In a field study on the LiWu River in Taiwan, Hartshorn *et al.* (p. 2036) found that it is the everyday flows that are mainly responsible for deepening of the bedrock channel in this region of active mountain building. The huge floods act primarily to widen the channel and induce hillslope collapse.

Forest Refuges

Climatic fluctuations during the Pleistocene caused large-scale vegetation changes in temperate regions. Nevertheless, genetic evidence suggests the existence of refugia where populations of plant species persisted unscathed. A finely detailed pollen analysis of sediments from the Ioannina basin in northwestern Greece by Tzedakis *et al.* (p. 2044; see the Perspective by Taberlet and Cheddadi) confirm the existence of such refugia in southeastern Europe. Populations of oak, pine, fir, beech, and other tree species persisted through 130,000 years in the Pindus mountains, apparently because local climatic conditions acted as a buffer.

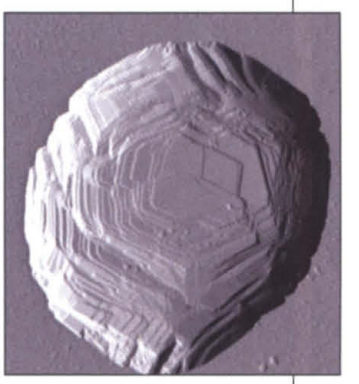
The Ins and Outs of Bacterial Proteins

In Gram-negative bacteria, secreted and membrane proteins are targeted to a protein conducting pore in the cytoplasmic membrane, the SecYEG translocon. The adenosine triphosphate (ATPase) SecA cycles between soluble and membrane-bound forms and in an ATP-dependent manner extrudes pre-proteins through the translocon. Hunt *et al.* (p. 2018) determined the crystal structure of soluble SecA with and without Mg-ADP bound at 3.0 and 2.7 angstrom resolution, respectively. Potential pre-protein binding sites are located on a surface that has been implicated in SecYEG binding. The authors propose that nucleotide hydrolysis and release are coupled to a domain-dissociation reaction that gates the binding of SecA to SecYEG.

How Anthrax Murders Macrophages

Selective destruction of activated macrophages is central to the pathogenicity of *Bacillus anthracis*. Park *et al.* (p. 2048) report that lethal factor (LF) produced by the bacterium specifically inactivates the p38 mitogen-activated kinase signaling cascade only in activated mouse macrophages, thus causing cell death. This inhibition prevents the expression of a subset of target genes of the transcription factor nuclear factor B that functions in macrophage survival. This toxic effect of LF on the immune system may play a major role in the virulence of *B. anthracis*. X

One Speck Is All It Takes



CREDIT: THÜRMER *ET AL.*

Most metals tarnish quickly in air, but under very low pressure conditions, many metals absorb oxygen but fail to oxidize. Thürmer *et al.* (p. 2033; see the Perspective by Over and Seitsonen) used scanning tunneling microscopy to show that for lead, impurities are the key to oxidation. Clean lead crystallites, even at elevated temperatures, did not oxidize after exposure to many monolayers of oxygen. By changing temperatures slightly, the shape of the crystallite could be changed, and this process could expose impurities. The unburied impurities rapidly nucleated lead oxide. An analysis of the oxide growth shows how the oxide, once formed, catalyzes its own growth.

The Cost of Being Bigger

In most mammal species, competition between males for female partners has led to sexual size dimorphism (SSD)—that males are usually larger. Males also tend to die sooner than females, and

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CONTINUED ON PAGE 1955

PIERCE

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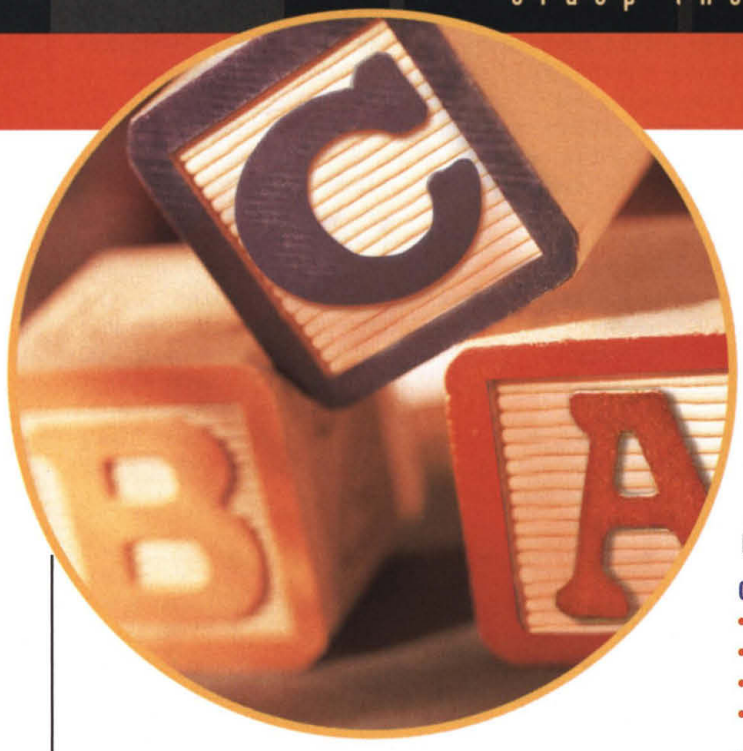

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U.S. Patent # 4,839,295

1. Smith, P.K., *et al.* (1985). Measurement of protein using bicinchoninic acid. *Anal. Biochem.* **150,** 76-85.

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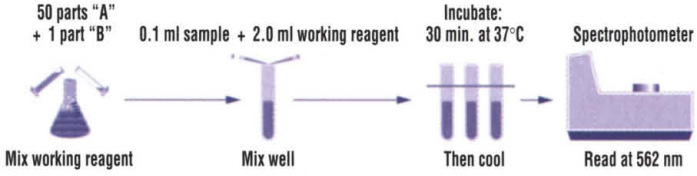

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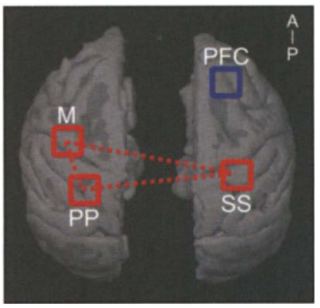
while male aggression takes its toll, some studies suggest that differences in parasite load between males and females are also to blame. Moore and Wilson (p 2015; see the Perspective by Owens) performed a meta-analysis across many species and found that male-biased parasitism is predictable and depends on the extent of sexual selection, as measured by either mating system or the degree of SSD. Across species, sex differences in parasite loads were associated with sex differences in mortality.



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Leaving a Lasting Trace

The coding, storage, and reactivation of memories at the systems scale (for example, a reaching movement cued by a visual stimulus) has been thought to involve the association of neural firing patterns across the different brain regions that subserve the various functions, such as visual and motor processing. Hoffman and McNaughton (p. 2070) have recorded simultaneously the activity of neural ensembles in four parts of the monkey brain throughout a reaching task. The distributed and correlated activity that occurred during the reaching movement can be detected in three of these regions (in the motor, somatosensory, and parietal cortices), but not in the prefrontal cortex, during a post-task rest period. These findings support the idea that concurrent network activity is the neural representation of a memory.

Haploinsufficiency Comes into Bloom

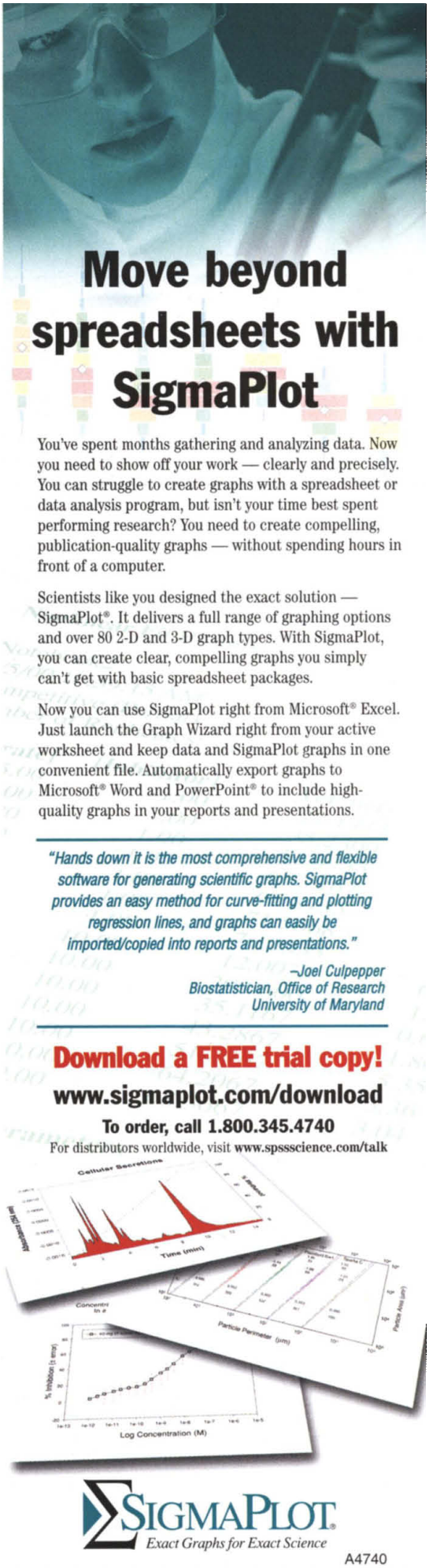
A widely accepted model of cancer genetics proposes that tumorigenesis requires inactivation of both alleles of a tumor suppressor gene. However, recent evidence from mouse models suggests that mutation of only one allele (producing "haploinsufficiency," a state in which the wild-type tumor suppressor is present at half its normal dose) may also affect cancer risk. Goss *et al.* (p. 2051) now report that mice show an enhanced susceptibility to tumor formation when they carry one mutant and one wild-type copy of *Blm,* the causative gene for the human cancer predisposition disorder Bloom syndrome. In a companion study of a human population, Gruber *et al.* (p. 2013) find that Ashkenazi Jews heterozygous for the same *BLM* mutant allele are more than twice as likely to develop colorectal cancer as control subjects.

Versatile Cytokines

Type 1 interferons (IFN-α and IFN-β) help defend against viruses through the activation of a variety of protective innate immune pathways. A more controversial mode of action proposed for these cytokines is that they might also regulate IFN-γ, the type 2 interferon responsible for directing the cell-mediated arm of the adaptive immune response. Nguyen *et al.* (p. 2063) now provide direct evidence that in addition to interleukin-12 (IL-12), IFN-α can activate the IFN-γ–dependent response to viral infection in mice. However, this process required activation of the signal transducer and activator of transcription (STAT)–4, which is also the primary target of IL-12. This finding refocuses the role of type-1 IFNs in controlling adaptive, as well as innate, immune responses to pathogens.

Runaway Mutations

Germinal centers (GCs) are transient structures within organized lymphoid tissue that are formed by the collaborative response of T and B lymphocytes to foreign antigen. Intense somatic antibody gene mutation (hypermutation) as well as antigen-driven cellular proliferation and death occur in GCs and select for B cells that produce high-affinity antibodies. It has also been assumed that GCs host equivalent events that lead to aberrant B cell responses to self-antigens and autoimmunity. Unexpectedly, William *et al.* (p. 2066; see the Perspective by Fu and Storb) found that in a background of mice known to possess a strong autoimmune phenotype, somatic hypermutation of genes encoding a self-reactive antibody occurred in regions adjacent to but distinct from GCs. This dissociation of extensive somatic mutation from GCs could reflect a critical element in the progression toward autoimmunity.



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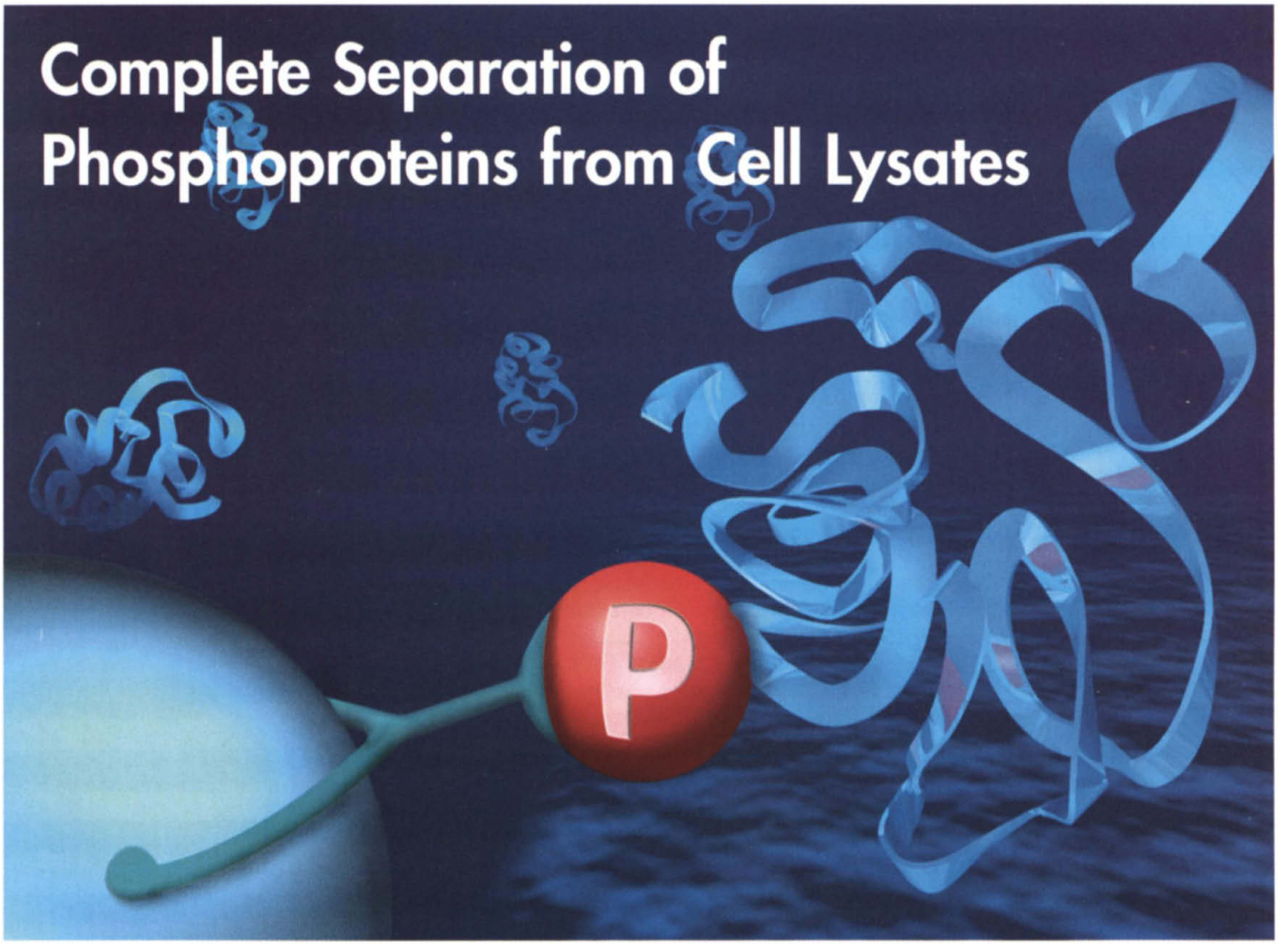

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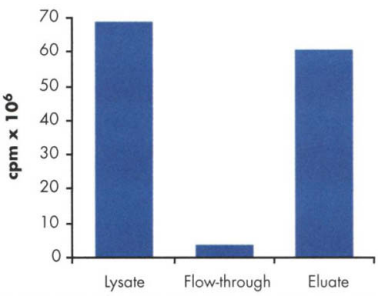

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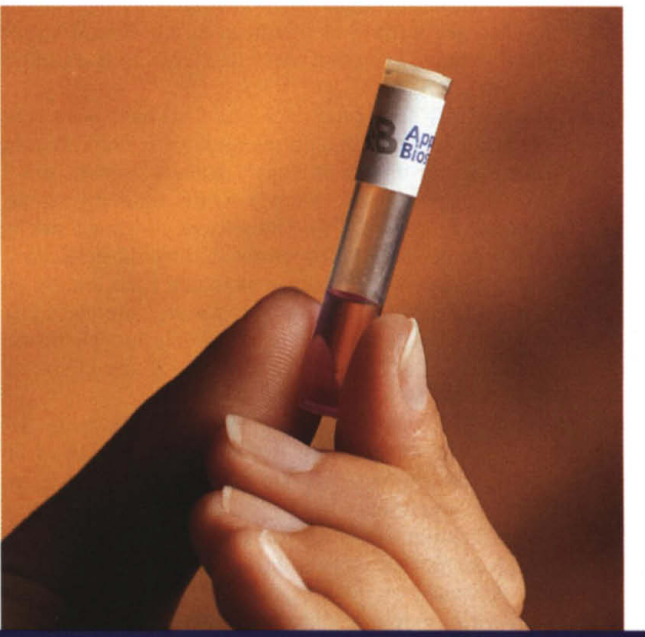

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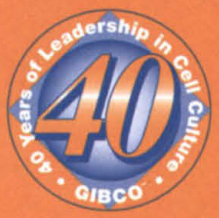

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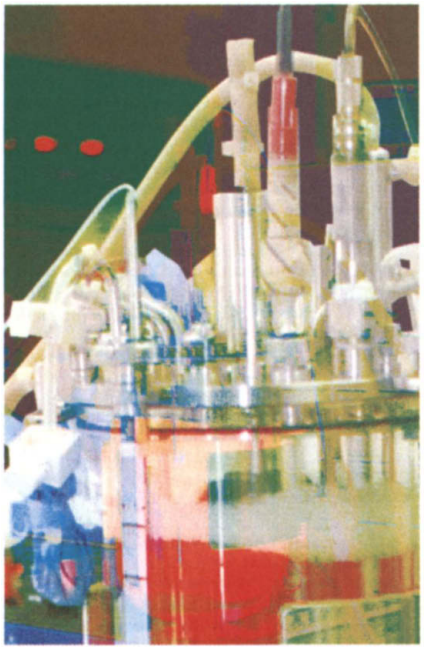

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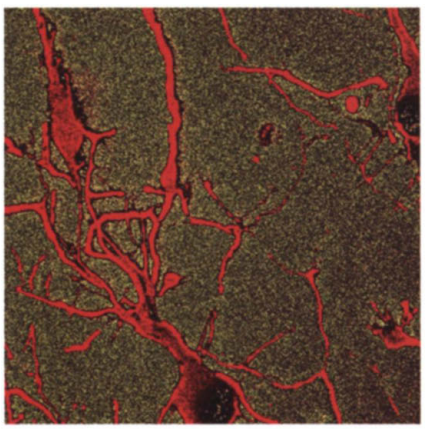

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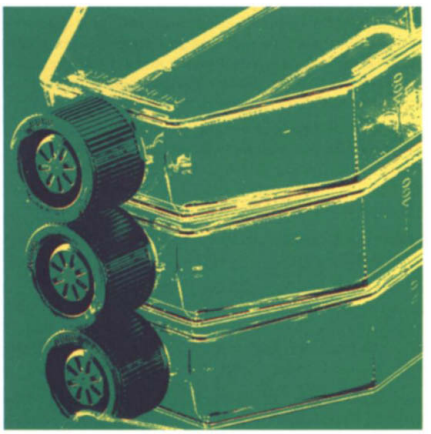

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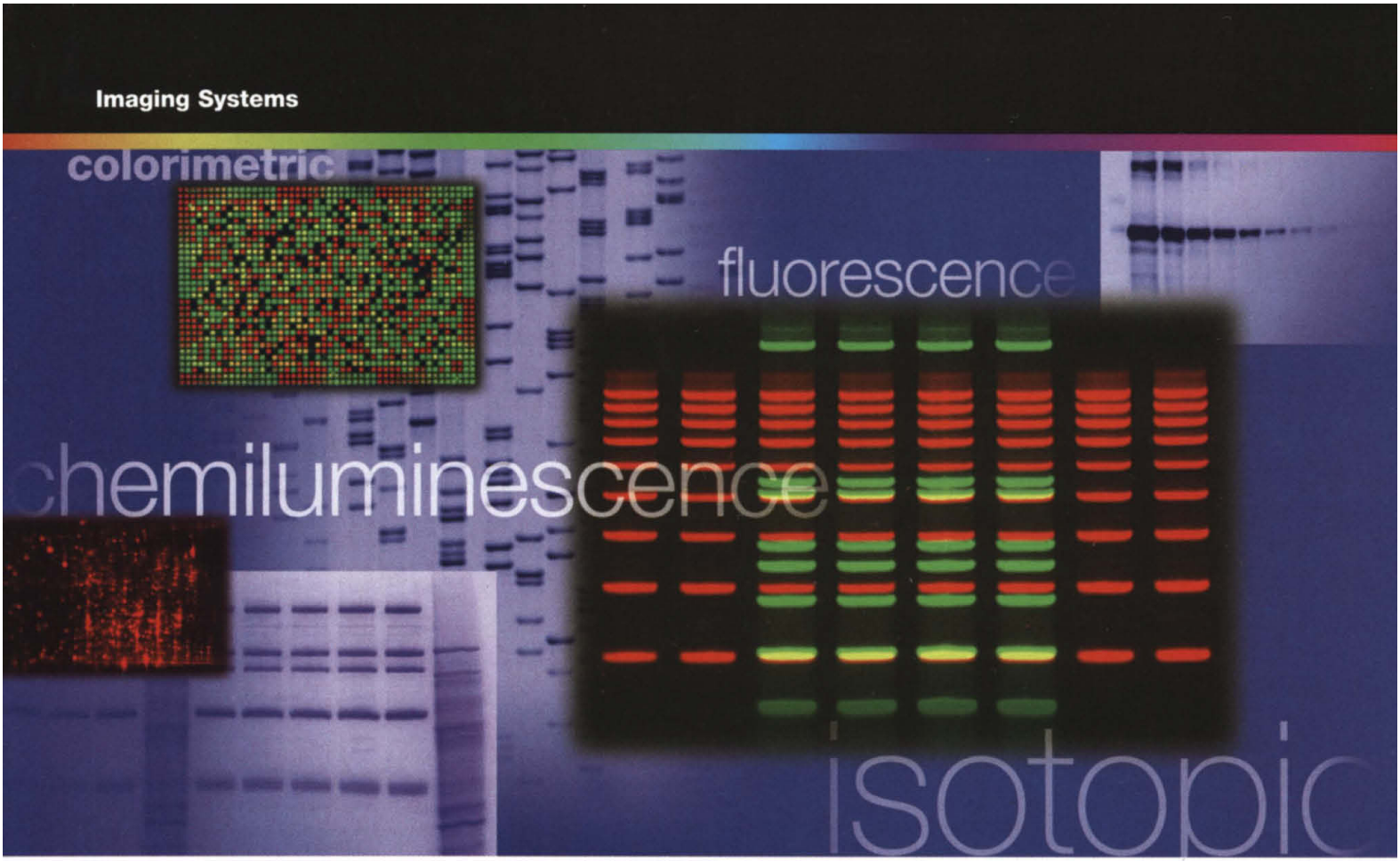

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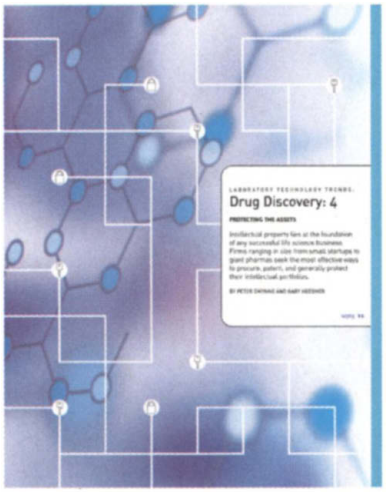

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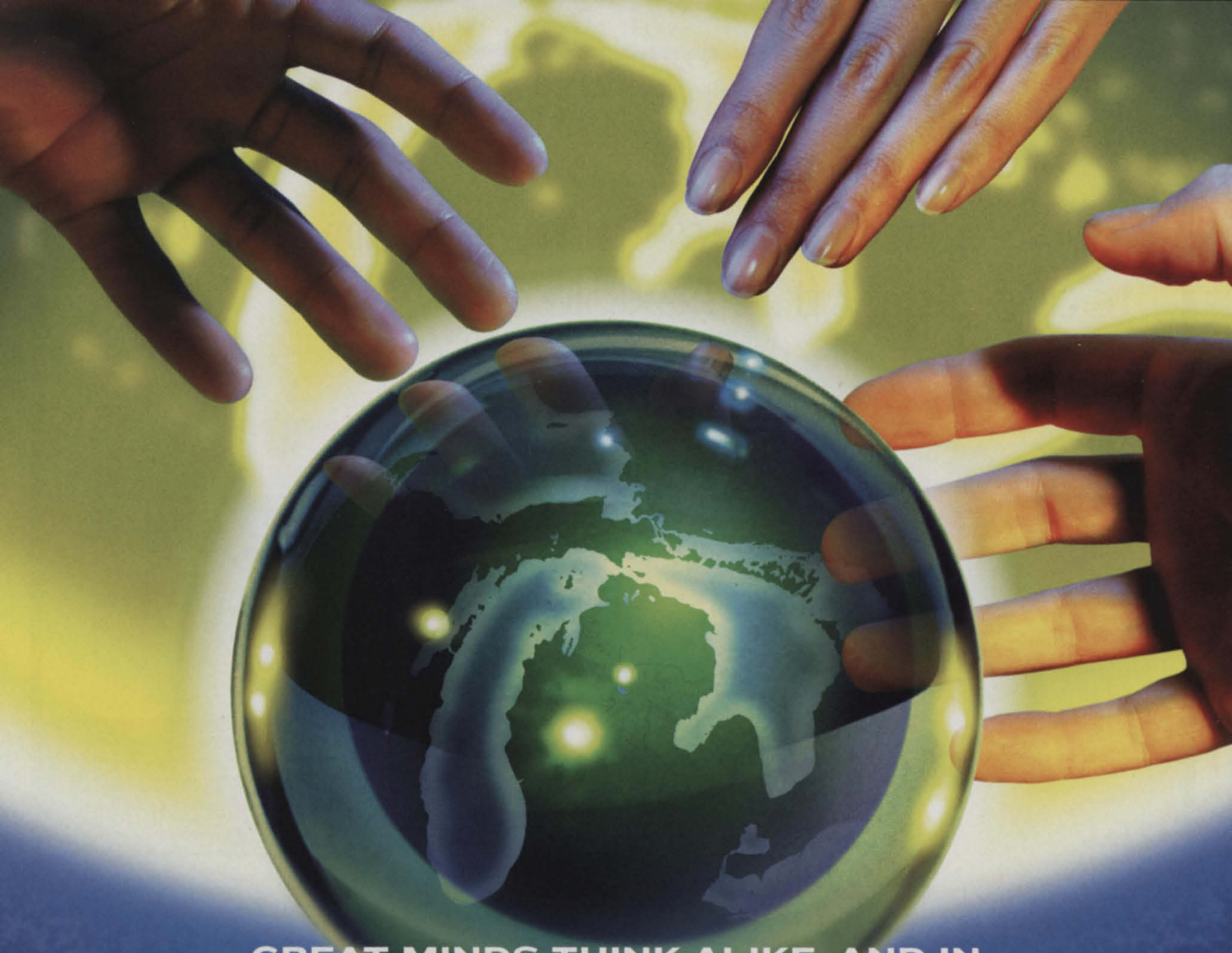

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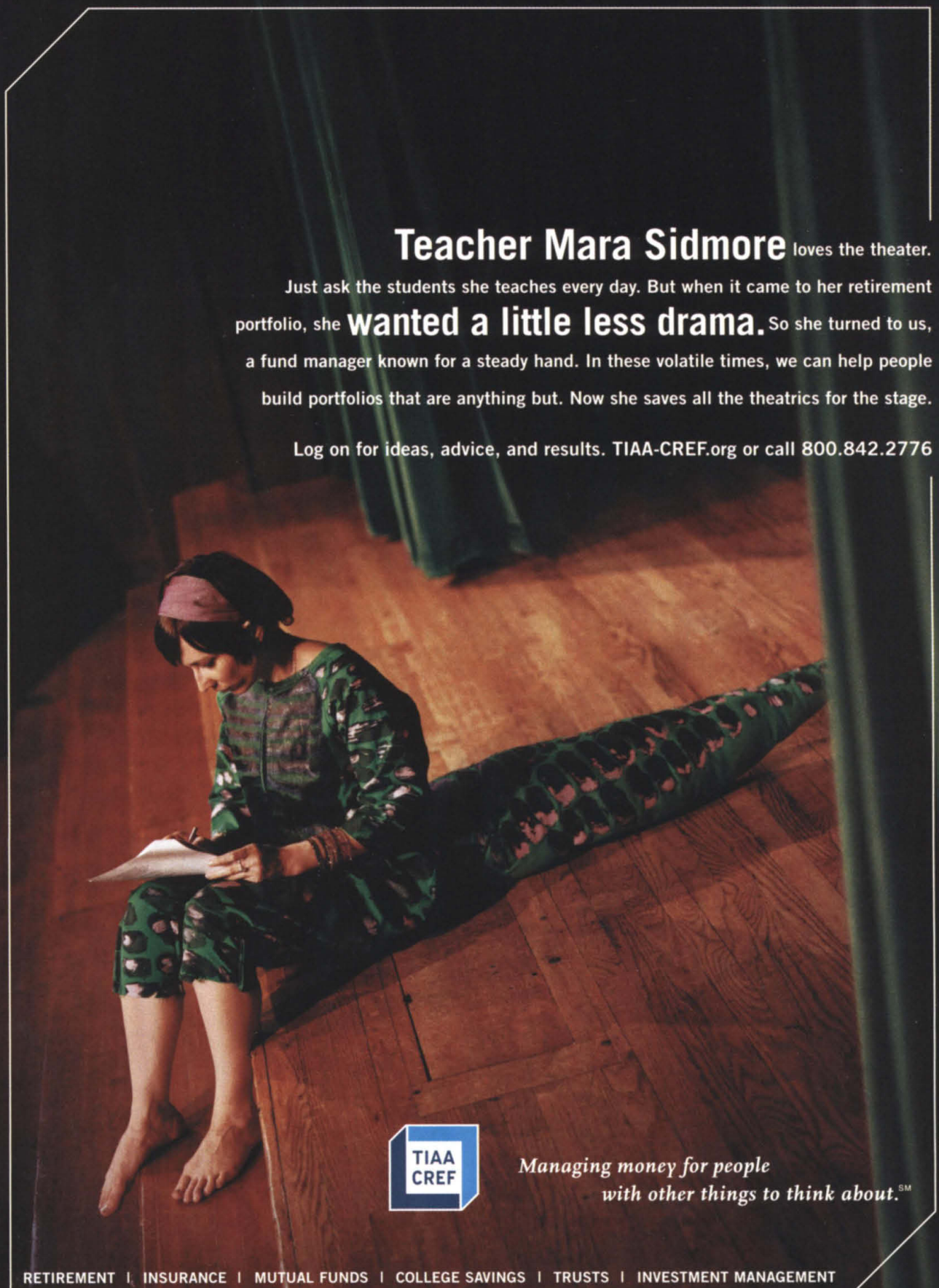

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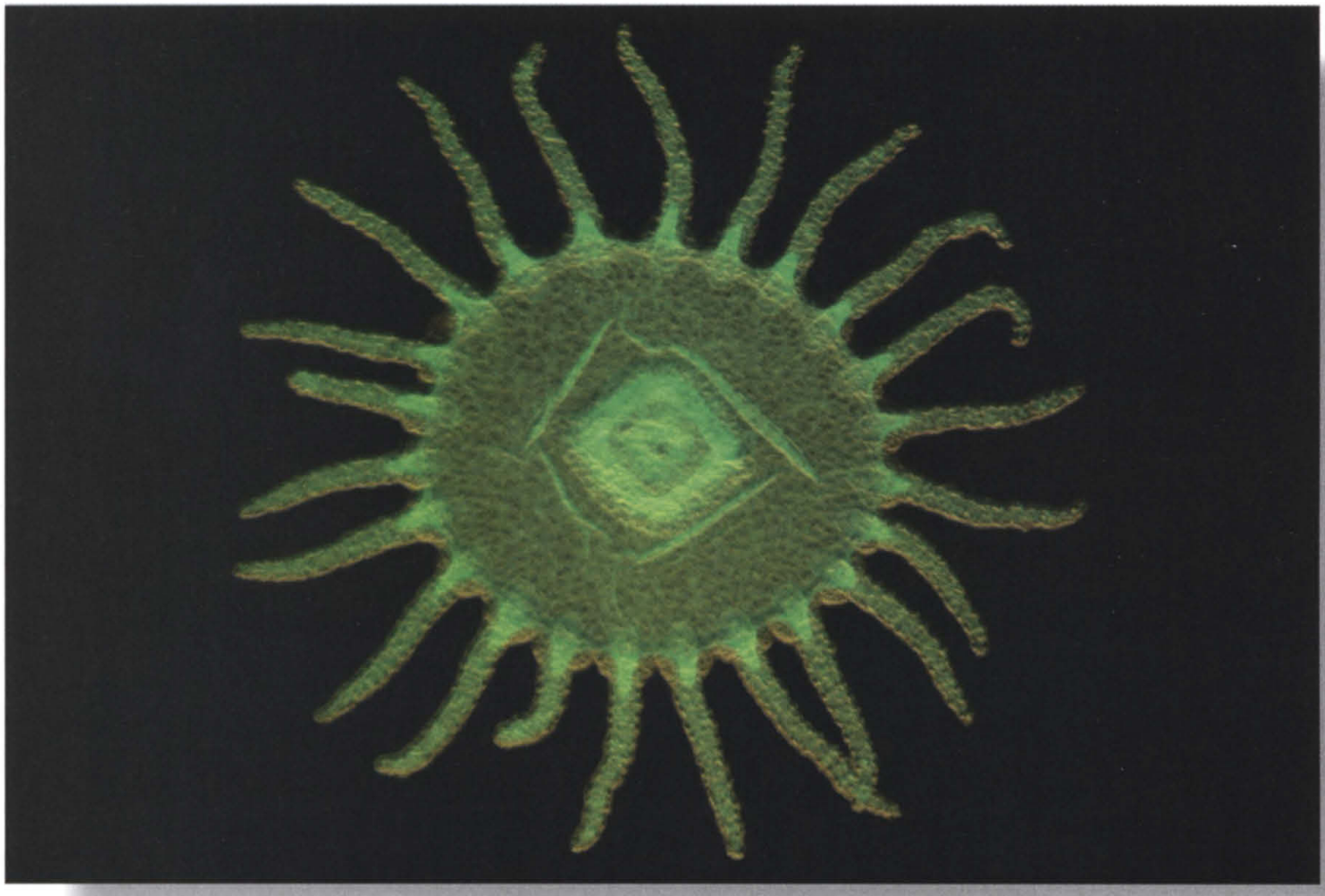

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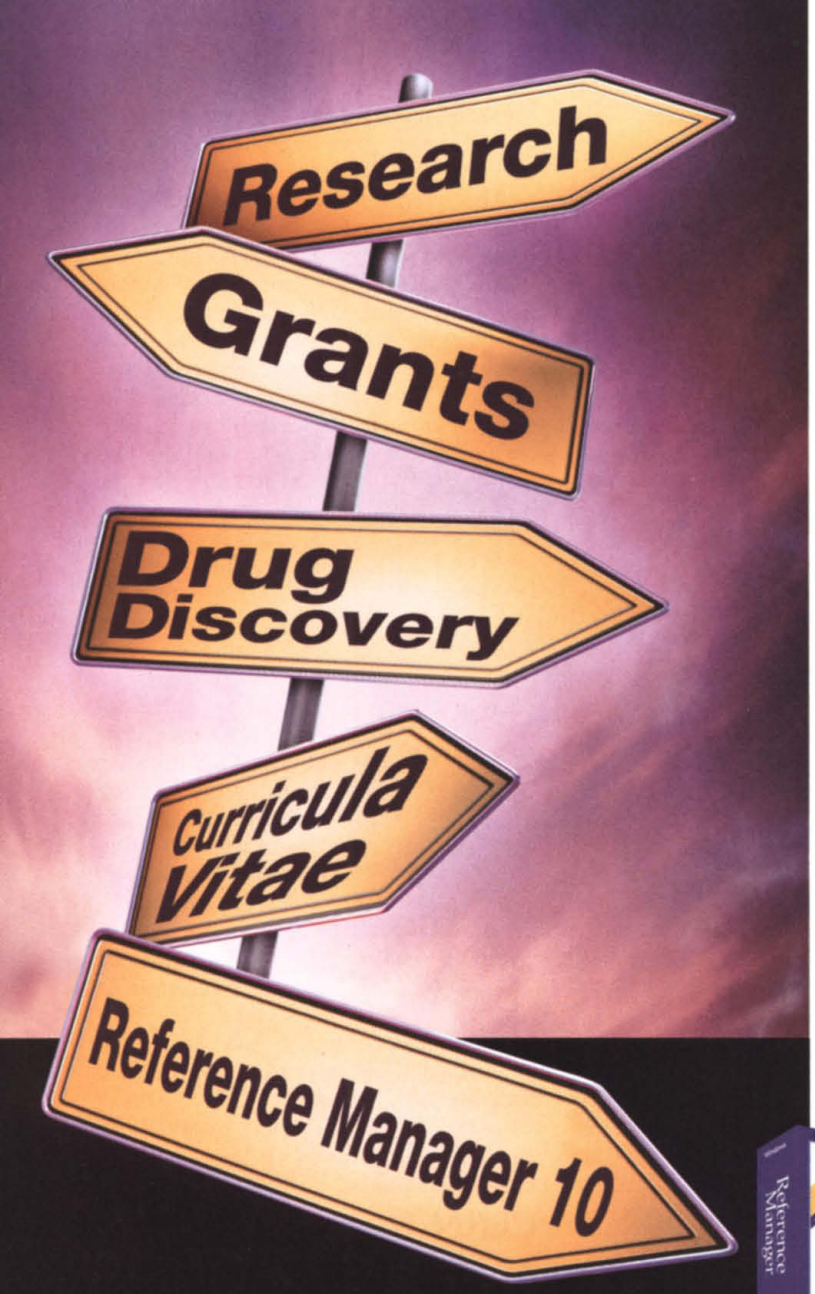

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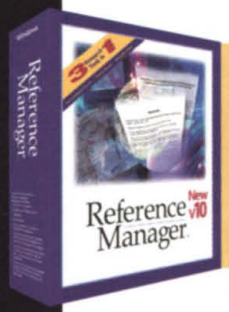

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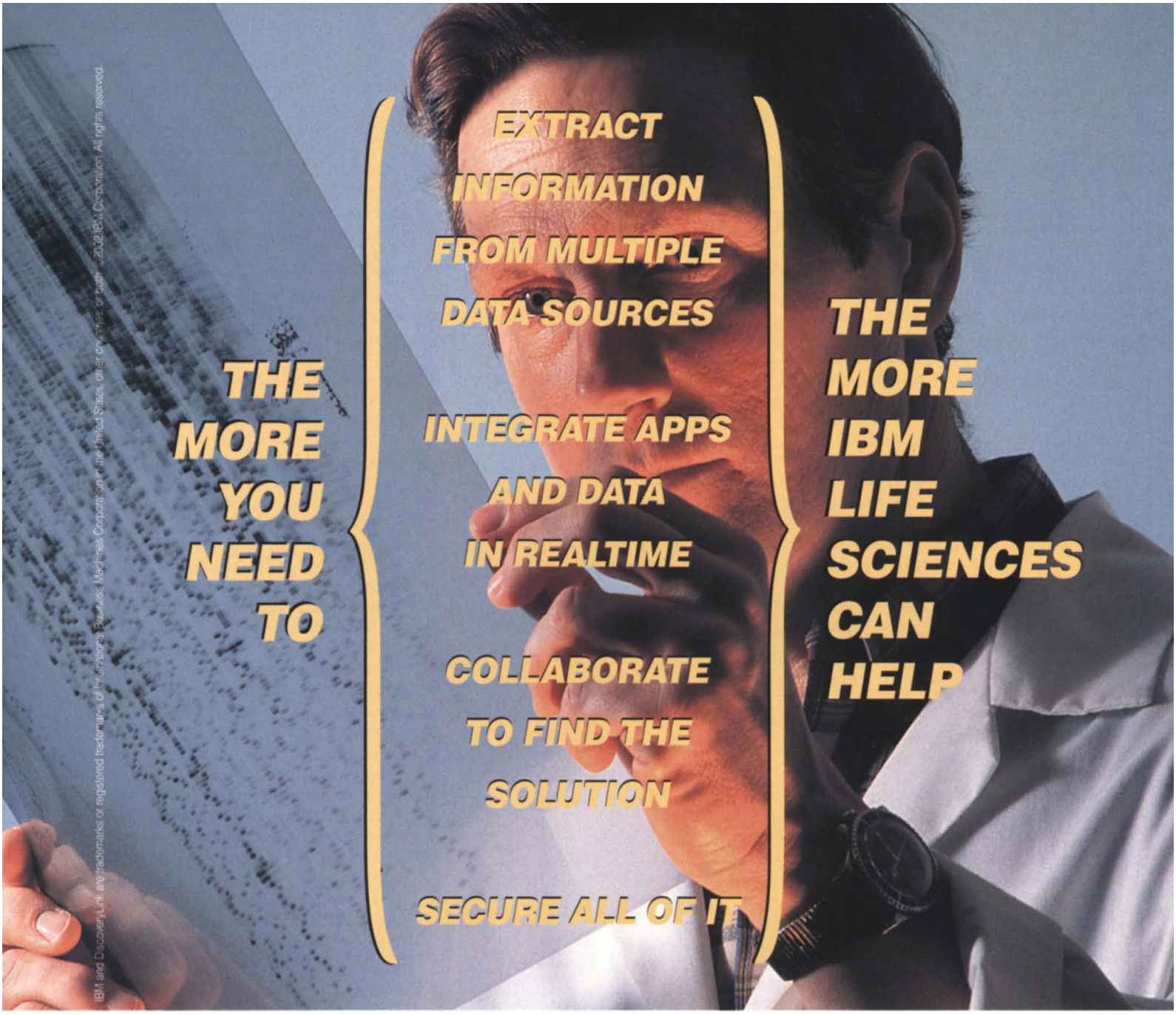

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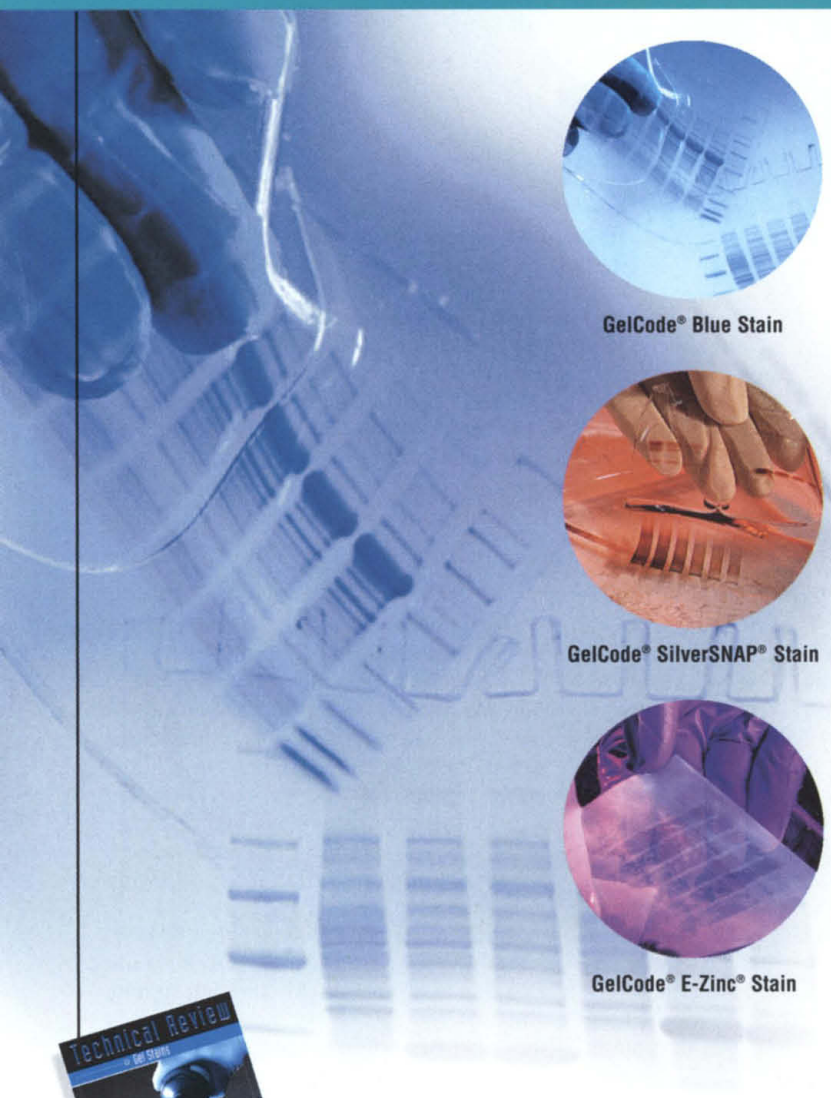

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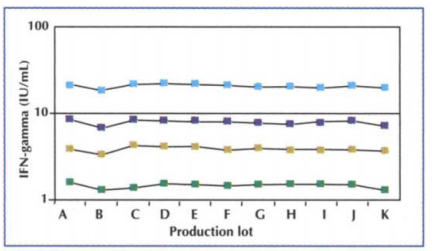

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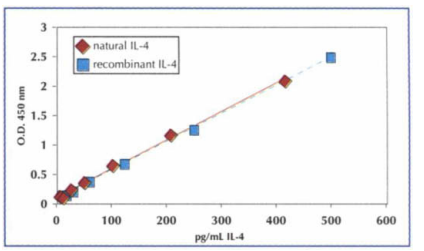

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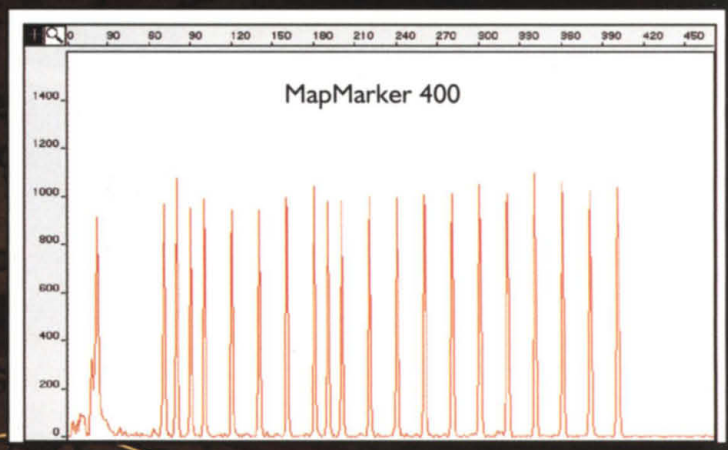

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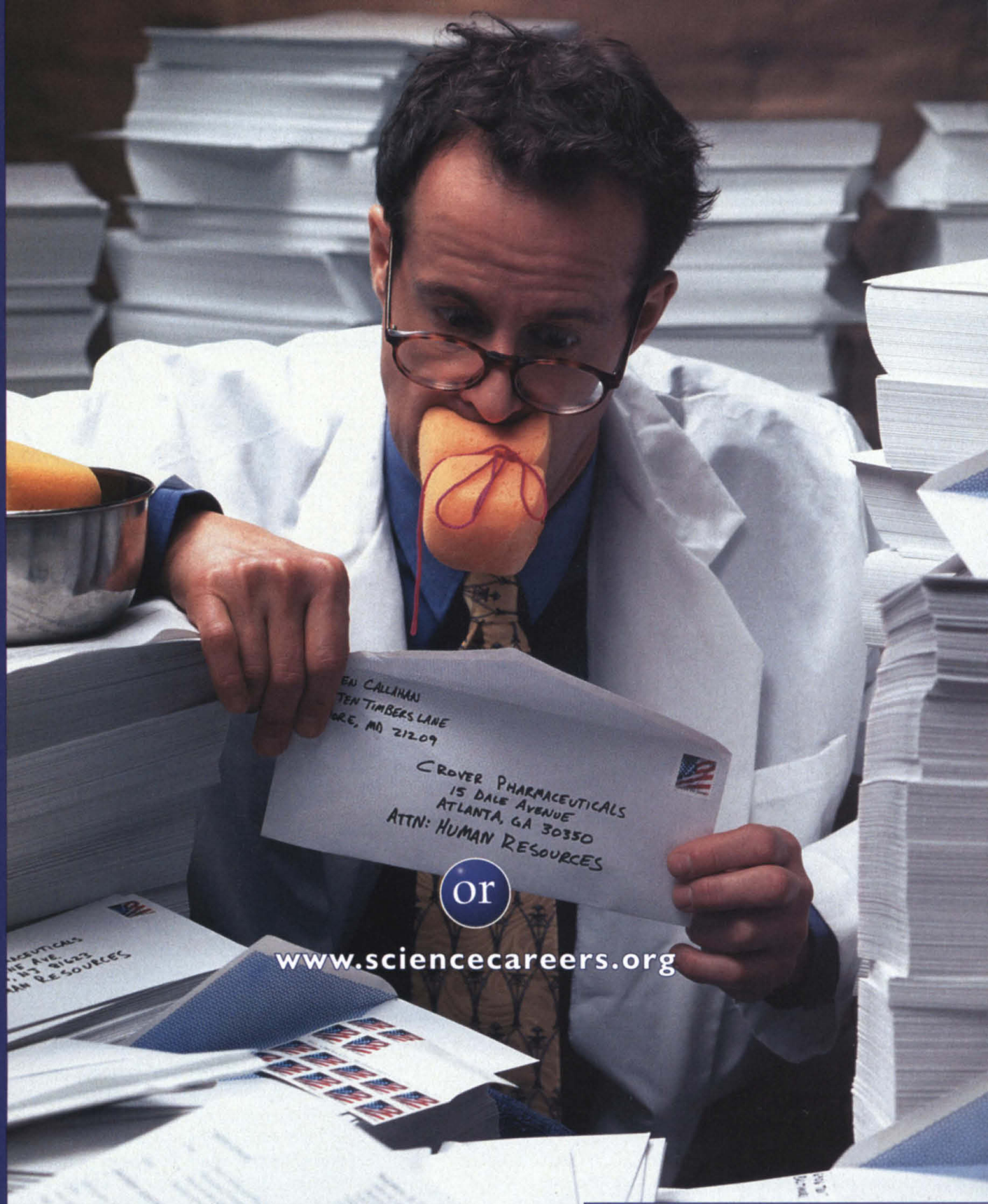

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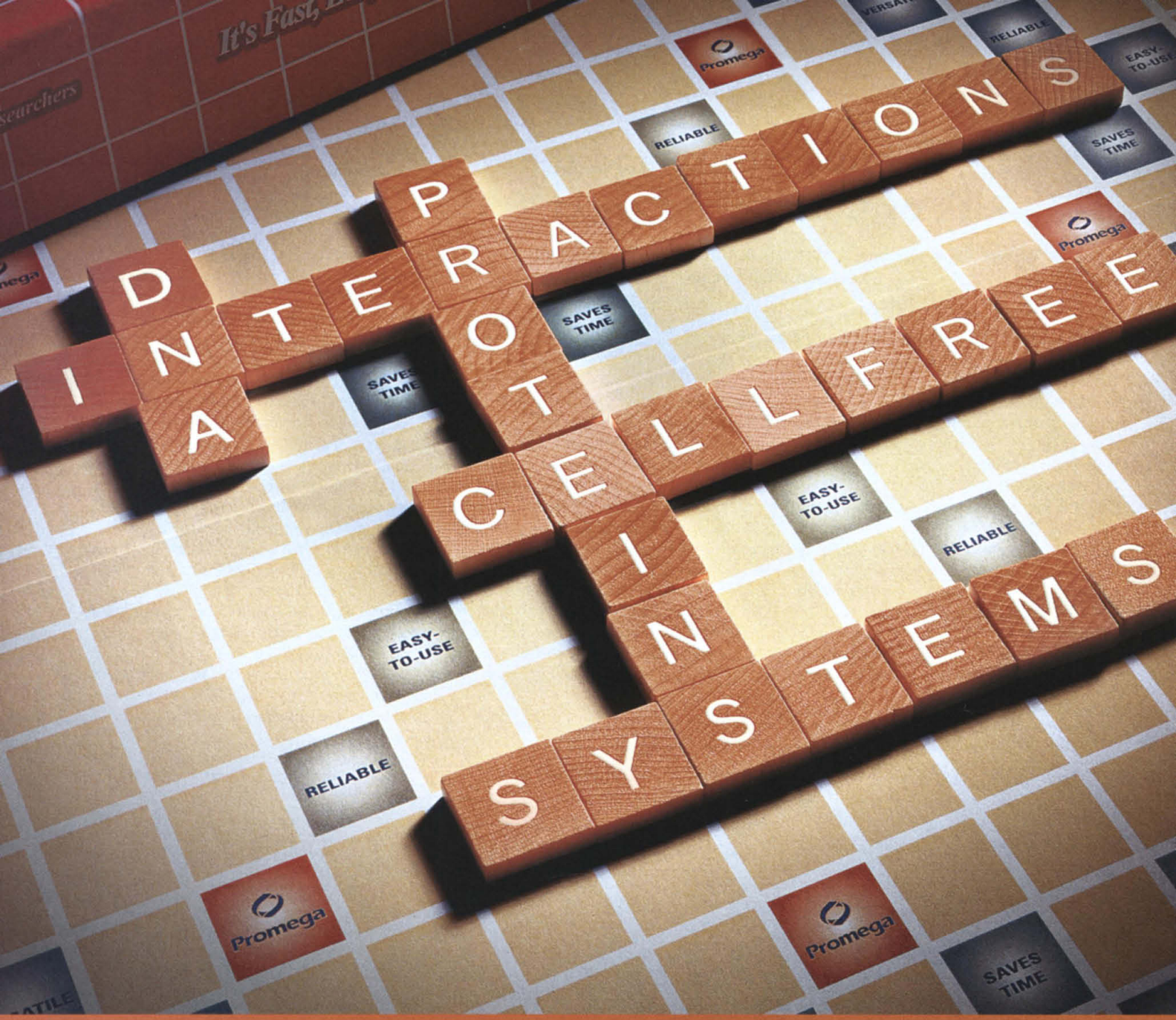

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