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SCIENCE

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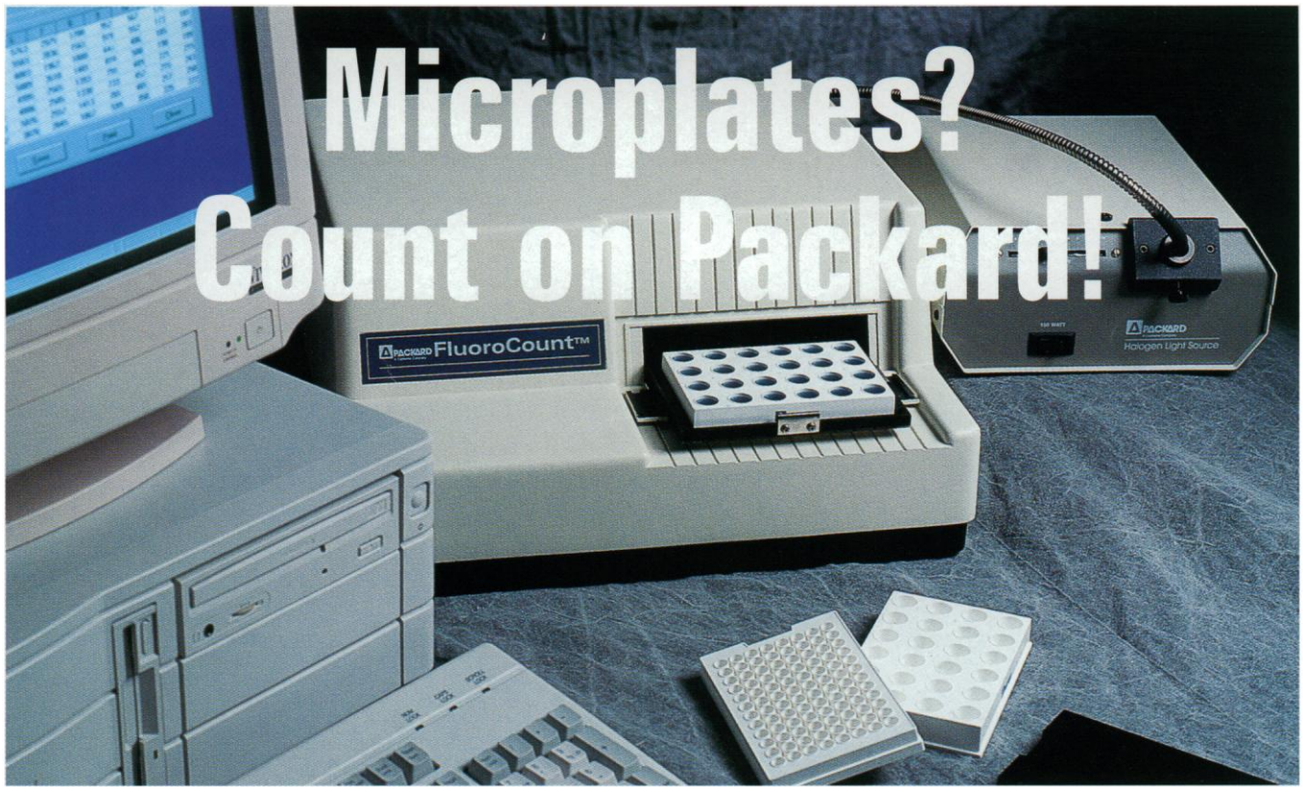
Frontiers in Cell Biology: *The Cytoskeleton*



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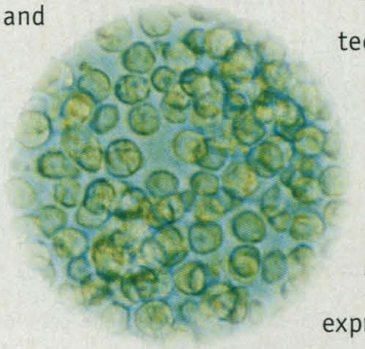

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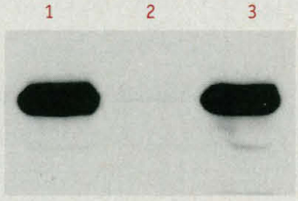

Western blot of constitutive, uninduced, and induced β-gal expressed with DES™

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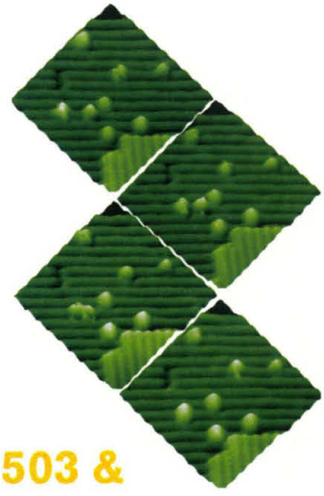
Guiding axons across the midline



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Dancing dangling bonds

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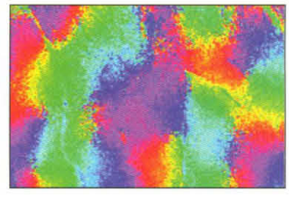
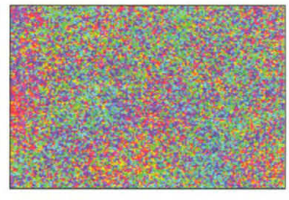
COVER

Quick freeze–deep etch electron micrograph of a mouse nerve axon showing a microtubule (25-nanometer diameter, linear tube-like structure) and a cross-bridge (perhaps the motor protein KIF) linking the microtubule and a membranous organelle. Microtubules are a major component of the cytoskeleton and serve as a type of rail along which motor proteins transport organelles inside cells (see page 519). This special issue, introduced by the Editorial on page 459, is devoted to the cell biology of the cytoskeleton. [Image: N. Hirokawa]

REPORTS

555
Bay invasion





566
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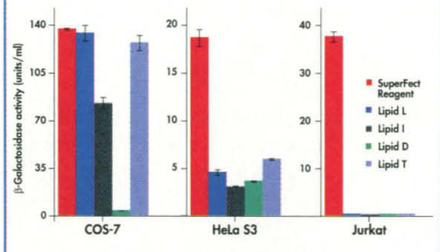
Comparison of Transfection Efficiencies



Comparison of transfection efficiencies obtained using SuperFect Reagent and four of the most commonly used liposome reagents. COS-7, HeLa S3, and Jurkat cells as indicated were transfected in 96-well format using 0.5 µg pCMVβ. 2 x 10⁴ cells were seeded per well one day prior to transfection. Transfection efficiencies are given as β-galactosidase units per ml. Each bar represents the average transfection efficiency from four replicates.

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edited by PHIL SZUROMI

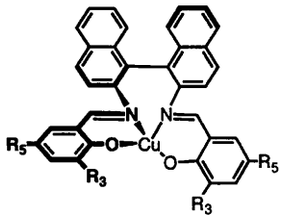
Polar wander and sea level

Changes in sea level affect the stratigraphy and facies of sediments deposited on continental margins. Analysis of particular seismic records of these sediments has allowed correlation of facies and sediment patterns in different basins and led to the possible recognition of many global (eustatic) changes in sea level. The origin of the longer term (tens of millions of years) variations in sea-level changes are uncertain and have usually been ascribed to changes in ocean spreading rates. Mound and Mitrovica (p. 534) use numerical simulations to propose instead that they are the result of the long-term wander of the rotational pole of the Earth that can affect sea level by up to 200 meters. In particular, the well-documented Cretaceous and Tertiary sea-level changes might be in part a result of the wander of Earth's rotation pole.

■

Complexes that mimic galactose oxidase

In metalloenzymes, the metal-containing sites and a few key residues may mediate catalysis,



but the protein matrix still plays an important role in minimizing side reactions. For this reason, small metal complexes that faithfully mimic the reactivity of metalloenzymes are rare. Wang *et al.* (p. 537; see the news story by Service, p. 479) have synthesized copper complexes that reproduce several features of the galactose oxidase, including the use of O_2 as a two-electron oxidant and the formation of a five-coordinate Cu(II)–phenoxyl radical as the active species, as well as Cα-H bond scission in the alcohols undergoing oxidation.

Mild route to ammonia

Conversion of dinitrogen (N_2) into ammonia requires special catalysts or extreme conditions or both; even the industrial Haber-Bosch process, which uses catalysts based on iron oxides, requires elevated temperatures and pressures to synthesize ammonia. Recently inorganic chemists have made metal complexes that activate N_2 in ways analogous to enzymes like nitrogenase. Nishibayashi *et al.* (p. 540; see the commentary by Leigh, p. 506) now show that a tungsten-dinitrogen complex can react with ruthenium complex and hydrogen at 1 atmosphere of pressure at 55°C to produce ammonia. Dihydrogen appears to produce a hydride that attacks N_2 to produce NH_3.

■

Surface imaging and adsorption mechanisms

Gas-phase molecules can adsorb onto surfaces and form strong bonds with the surface atoms; this chemisorption process can be a multistep process and can require particular surface sites. Two reports show how the scanning tunneling microscope can reveal insights into these processes (see the commentary by King, p. 503). More weakly bound precursor states to the chemisorbed state have been invoked in many surface science studies to explain several observations, such as the apparent ability of a molecule to remain on the surface as it moves about before finding an appropriate adsorption site. These extrinsic precursors, which are blocked from surface sites by previously adsorbed molecules, have been directly observed in earlier studies. Brown *et al.* (p. 542) provide direct evidence for the formation of intrinsic precursors, which form on bare surface sites. The molecules can rest in the same surface sites as the chemisorbed molecules in a weakly bound state, and they can be switched from one state to the other by changes in temperature or with an electric field. Thin film growth by chemical vapor deposition requires reactive sites near one another on the surface. Semiconductors such as silicon are usually terminated with hydrogen atoms; heating desorbs some H_2 and leaves reactive "dangling bonds," but these same elevated temperature conditions can cause the dangling bonds to diffuse away from each other. McEllistrem *et al.* (p. 545) studied the Si(100)-2×1 deuterium-terminated surface at elevated temperatures with a scanning tunneling microscope and show that while the dangling bonds do diffuse, they appear to be attracted to one another and recombine. This process produces a greater population of reactive pairs of dangling bonds.

■

Large pores to order

Mesoporous silica materials with hexagonally ordered pores ranging from 5 to 30 nanometers in diameter have been synthesized by using poly(alkylene oxide) triblock copolymers as templates. Zhao *et al.* (p. 548) describe how counterion-mediated synthesis conditions can lead to thicker pore walls (3 to 6 nanometers). These thicker walls are more highly ordered than those in other mesoporous silicates, and this ordering gives the material greater hydrothermal stability. The copolymer template can be removed by mild heating.

■

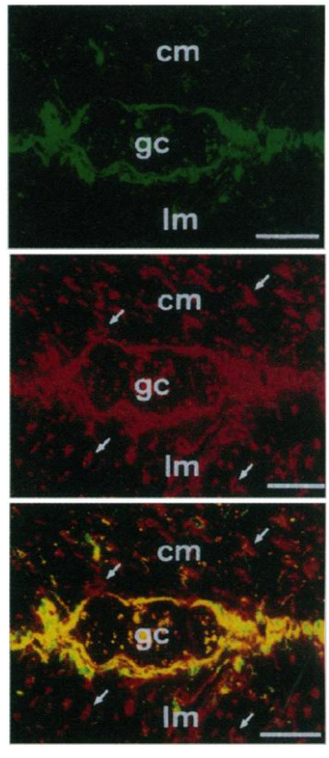
Organic lasers

Lasers based on small organic molecules have certain potential advantages over semiconductor lasers. including insensitivity to changes in operating temperature and ease of fabrication. Bulović *et al.* (p. 553) demonstrate an optically pumped vertical cavity laser that uses an organic semiconductor, Alq_3, whose emission is matched to the absorption of a laser dye. Narrow linewidths (0.6 angstrom), high output powers (3 watts), and long device operation lifetimes (10^6 laser pulses) were achieved. The mirror reflectors in such a device could provide a favorable geometry for electrically pumped lasers.

■

Tumorigenesis in the GI tract

Little is known about the molecular etiology and cellular origin of gastrointestinal stromal tumors



(GISTs), the most common mesenchymal tumor in the human digestive tract. Hirota *et al.* (p. 577) report that these tumors fre-

(Continued on page 455)

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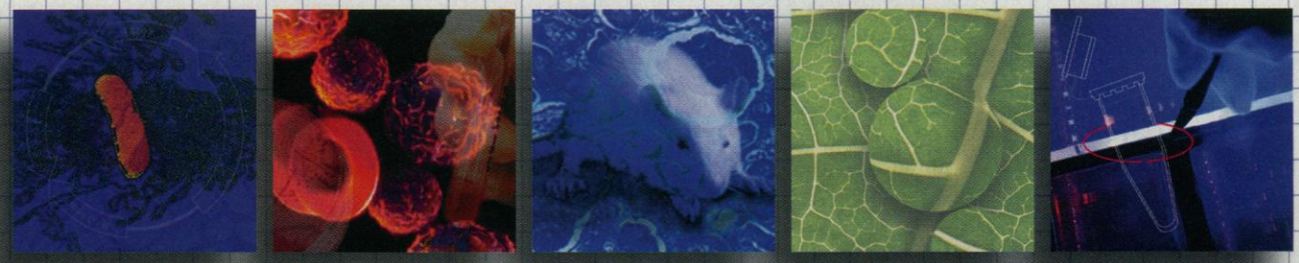

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(Continued from page 453)

quently express the c-*kit* receptor tyrosine kinase and that a subset of tumors have mutations in the c-*kit* gene. The mutant forms of kit have a constitutively active kinase and can induce malignant transformation of cultured cells. Co-expression of *kit* and the cell surface marker CD34 in the GISTs suggests that the tumors arise from interstitial cells of Cajal, a cell type that regulates autonomous contraction of the GI tract.

■

The melting pot

According to Cohen and Carlton (p. 555), the last 150 years have witnessed an almost complete alteration in the ecosystems of the San Francisco Bay and Delta. They identified more than 200 (as well as a further 125 cryptogenic species) exotic species, mostly ship-borne, and discovered several habitats that are wholly dominated by nonindigenous species in terms of number of species, individuals, and biomass. The rate of invasiveness is relentlessly increasing and is likely being mirrored in other estuaries around the world as a hidden cost of increasing international trade.

■

Predicting prostate cancer risk

Insulin-like growth factor–I (IGF-I) stimulates growth and inhibits apoptosis of prostate epithelial cells. To investigate whether serum IGF-I levels correlate with prostate cancer risk, Chan *et al.* (p. 563; see the news story by Barinaga, p. 475) conducted a case-control study of men enrolled in the Physicians' Health Study. IGF-I levels were measured in blood samples from 152 control men and 152 men who were diagnosed with prostate cancer an average of 7 years after providing their blood sample. Men in the highest quartile of IGF-I had a 4.3 times greater risk of developing prostate cancer than men in the lowest quartile, regardless of their baseline level of prostate-specific antigen (PSA). These results suggest that combined assessment of IGF-I and PSA may be a better predictor of prostate cancer risk than PSA alone.

■

Seeing is reorganizing

Optical imaging has made it feasible to follow the orientation specificity of neurons in the cat visual cortex during postnatal development, as well as to determine the properties and organization of ocular dominance and orientation columns. Crair *et al.* (p. 566) find that the columnar pattern of orientation specificities exists at birth and shows the effect of experience (visual deprivation) only at ages older than 3 weeks. The initial pattern of contralateral dominance becomes balanced only as a result of experience because it persists in visually deprived cats. Thus, the role of visual experience is to strengthen and equilibrate responses of already organized visual cortical neurons.

■

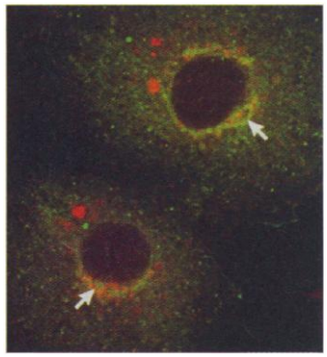
Layers of regulation

The Ras small guanosine triphosphatases (GTPases) are critical regulators of cell growth in response to mitogenic signals. Activation of Ras results in changes in the cytoskeleton that are mediated by another small GTPase known as Rac. Two reports present experiments that reveal the mechanism by which activated Ras leads to activation of Rac and document an important role of phosphoinositide 3-kinase (PI 3-K) in this signaling pathway. Nimnual *et al.* (p. 560) found that truncated versions of the protein Sos, which enhances nucleotide exchange on (and thus activates) Ras, activated Rac as well, but this effect required activation of PI 3-K by Ras. Similarly, Han *et al.* (p. 558) report that activity of Vav, another exchange factor for Rac, was inhibited by substrates of PI 3-K and enhanced by a phospholipid product of that enzyme, phosphatidylinositol-3,4,5-trisphosphate. This enzyme apparently binds directly to similar regions known as pleckstrin homology domains on Sos and Vav and provides, along with protein phosphorylation, a second layer of regulation of the exchange factors.

■

Dynamin in Golgi export

The role of dynamin in scission of clathrin-coated vesicles at the plasma membrane is now widely accepted. Jones *et al.* (p. 573) show that the dynamin family also plays a role in the formation of transport vesicles—both constitutive and clathrin-coated—upon exit from the trans-Golgi network. In a cell-free assay, antibodies to dynamin inhibited vesicle formation at the trans-Golgi

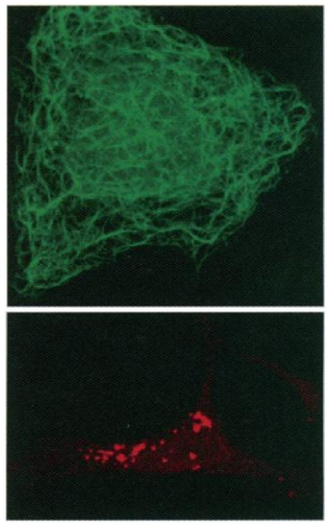


network. Thus, the dynamin family is important for multiple scission events in endocytic and exocytic membrane traffic.

■

Golgi motor

Membrane-bound organelles and vesicles can be transported around cells along cytoskeletal tracks, and these processes are usually regulated by members of the Rab family of small guanosine triphosphatases (GTPases). Echard *et al.* (p. 580) describe a protein found on the Golgi complex related to the molecular motor



kinesin that inhibits the effects of the GTP-bound form of Rab6. This membrane-bound protein, termed Rabkinesin-6, is likely to play a role in the control of membrane traffic through the Golgi complex.

■

Stifling stimuli

In the classical conditioning paradigm, as applied to reflexive eyeblink in rabbits, a strongly predictive conditioned stimulus (a tone) can inhibit or block the acquisition of conditioned responses to a second stimulus (a light) even if it predicts equally well the unconditioned stimulus (an airpuff). The cognitive interpretation of this phenomenon is that no additional information is provided by the second conditioned stimulus and that there is nothing new to be learned. Kim *et al.* (p. 570) suggest that the cerebellum, which mediates the eyeblink response, suppresses input coming from the inferior olive as conditioning occurs, thus blocking any association of the second conditioning stimulus with the same airpuff.

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*U.S.Patent 5,436,149 for LA Technology Owned by TAKARA SHUZO CO.,LTD

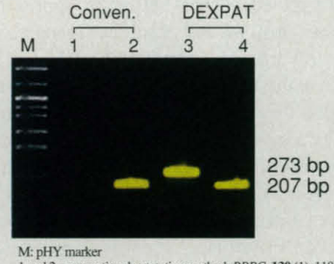
DNA Amplification from Histologic Sections

With DEXPAT™, DNAs were extracted as PCR ready templates which were then amplified with *Ex Taq* to result in excellent PCR amplification with greater yield and longer extension than the conventional method.

Comparison of Section Preparations
for K-*ras* 12 (107 bp) and ß-globin (408 bp and 262 bp) Amplification from Human Tonsil: 1 µl or 2.5 µl extracts used for 25 µl PCR

lane M:pHY marker
1 : paraffin-embedded, 1µl
2 : paraffin-embedded, 2.5 µl
lane 3 :frozen, 1µl
4 : frozen, 2.5 µl
5 : negative control

Comparison of Extraction Methods
for p53 *exon* 5 (273 bp) and *exon* 6 (207 bp) Amplification from Paraffin-embedded Tissues of Colon Cancer After a 10-year Preservation



lane M: pHY marker
1 and 2 : conventional extraction method: *BBRC* **130** (1), 118-126 (1985)
3 and 4: newly developed TaKaRa DEXPAT™ method

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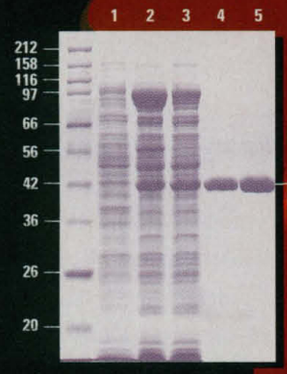

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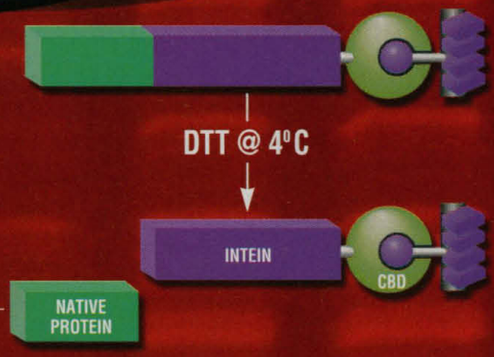
Lane 1: uninduced cell extract. Lane 2: induced cell extract showing expressed fusion protein (97 kDa). Lane 3: Flow through. Lane 4 and 5: MBP fractions eluted after inducing cleavage overnight at 4°C.



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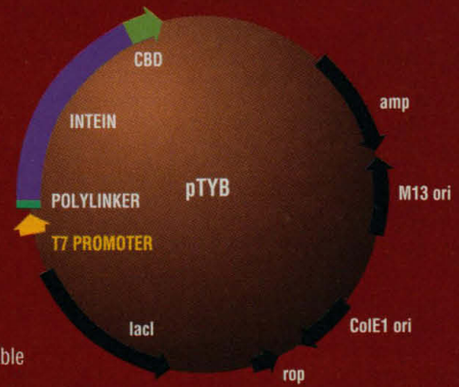

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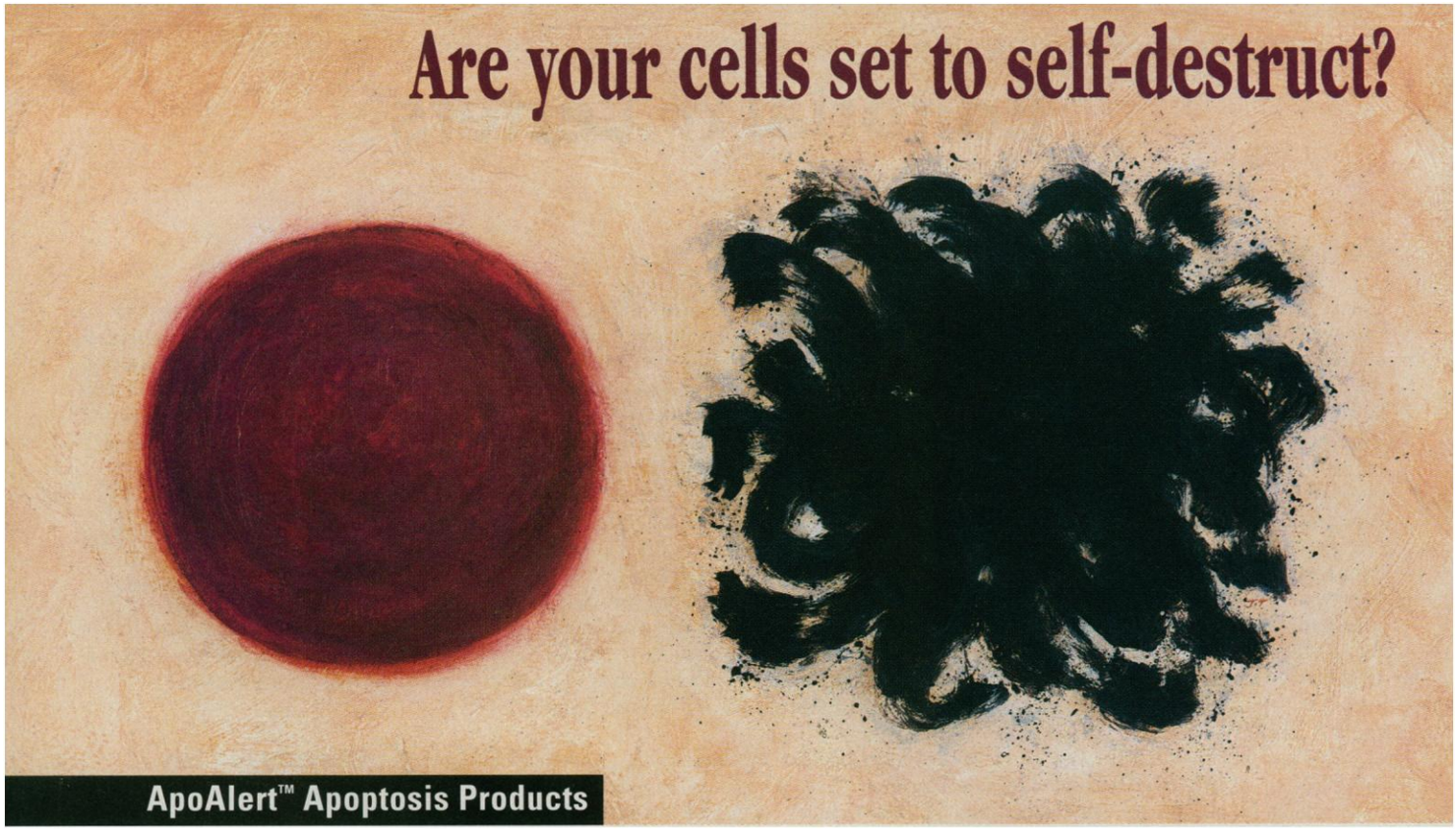
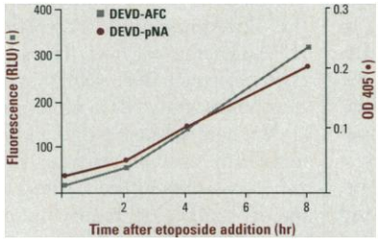
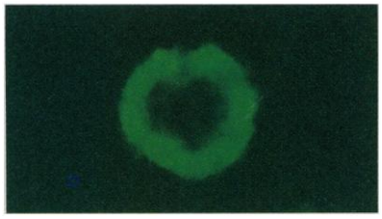


ApoAlert™ Apoptosis Products



ApoAlert CPP32 Protease assay detects CPP32 activity soon after induction of apoptosis.



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THE MERRILL LYNCH FORUM ANNOUNCES THE INNOVATION GRANTS COMPETITION

The Merrill Lynch Forum will award $150,000 in grants to recent Ph.D. recipients from universities worldwide. Top prize is $50,000.

In the 21st-century global economy, we believe that universities will be more important incubators of innovation and creators of intellectual capital than ever before. The Innovation Grants Competition seeks to encourage Ph.D. candidates to explore the marketplace potential of their dissertation ideas. In addition to cash awards, winners will meet with leading entrepreneurs and venture capitalists to discuss their work. The winning candidates' university departments will also receive $5,000 Innovation Grants.

All Ph.D. candidates in the sciences, liberal arts and engineering who successfully defend a dissertation between January 1, 1996 and May 31, 1998 are eligible to enter the competition. Awards will be announced in September, 1998. Applications and entry information can be obtained from the Forum Web site at www.ml.com/innovation or via e-mail to InnovationGrants@ml.com. Or call 1-888-33-FORUM.

An independent panel of distinguished scientists and entrepreneurs, under the direction of **Michael Schrage,** Research Associate of the MIT Media Lab, will judge the competition:

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Edgar W.K. Cheng, M.D., Chairman, World-Wide Investment Company Limited and Former Chairman, The Stock Exchange of Hong Kong

John Doerr, Partner, Kleiner Perkins Caufield & Byers

Esther Dyson, EDventure Holdings, Inc.

Peter Goldmark Jr., President, The Rockefeller Foundation

William Haseltine, Ph.D., Chairman & CEO, Human Genome Sciences, Inc.

John Markoff, Technology Correspondent, *The New York Times*

Edward McKinley, President, E.M. Warburg, Pincus & Company, International, Ltd.

Arati Prabhakar, Ph.D., Chief Technology Officer, Raychem Corp.

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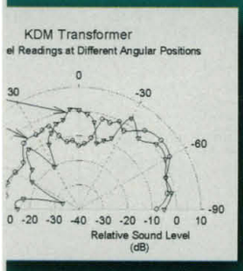

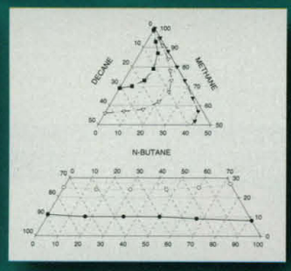

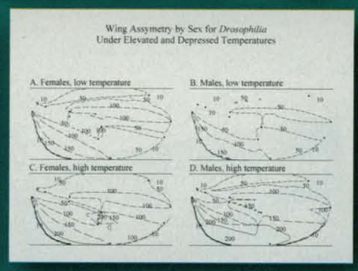

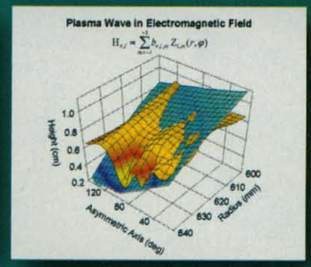

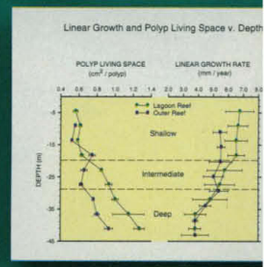

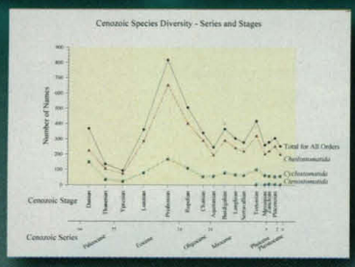

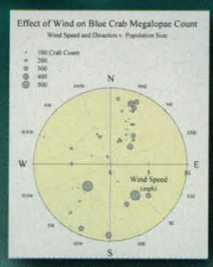

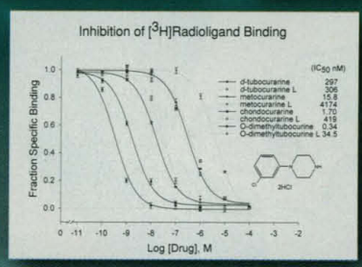

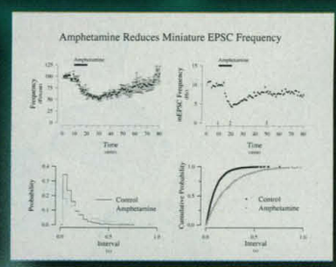

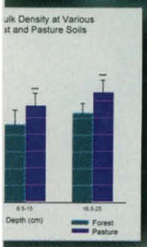

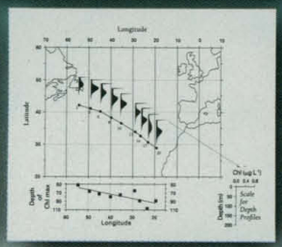

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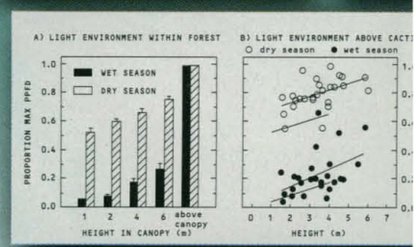

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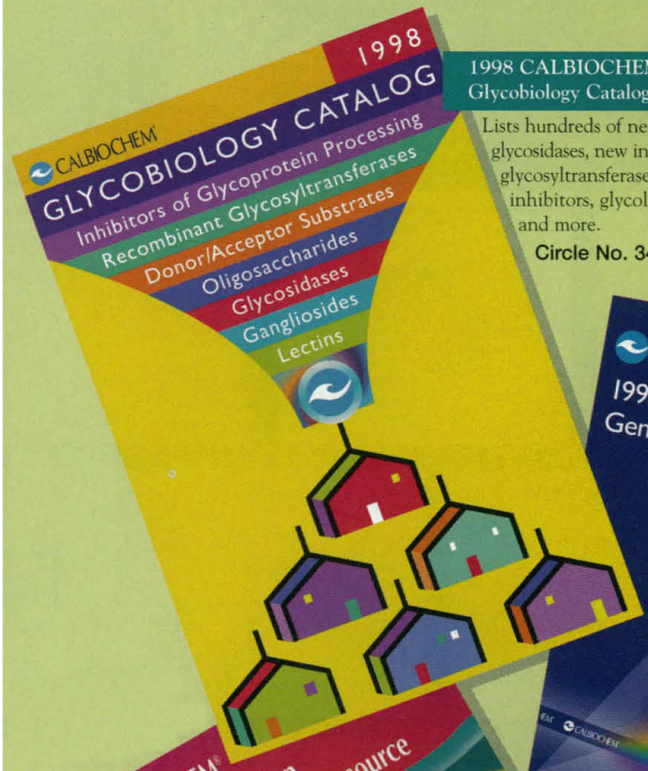

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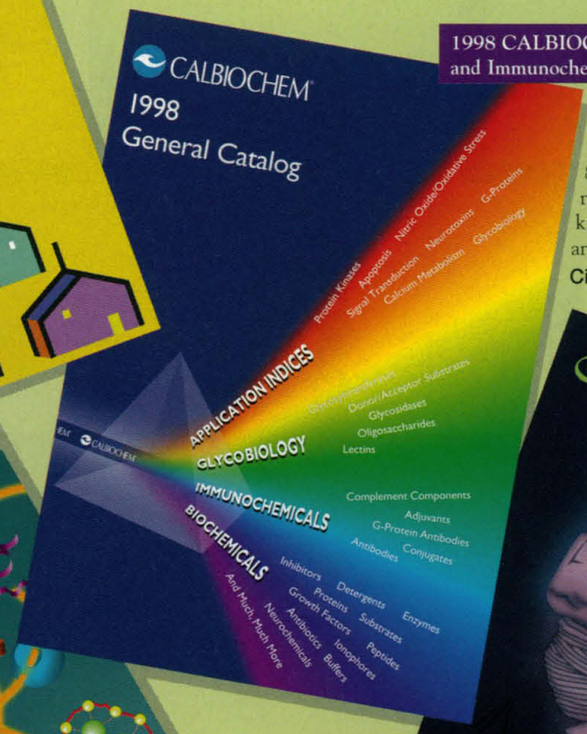

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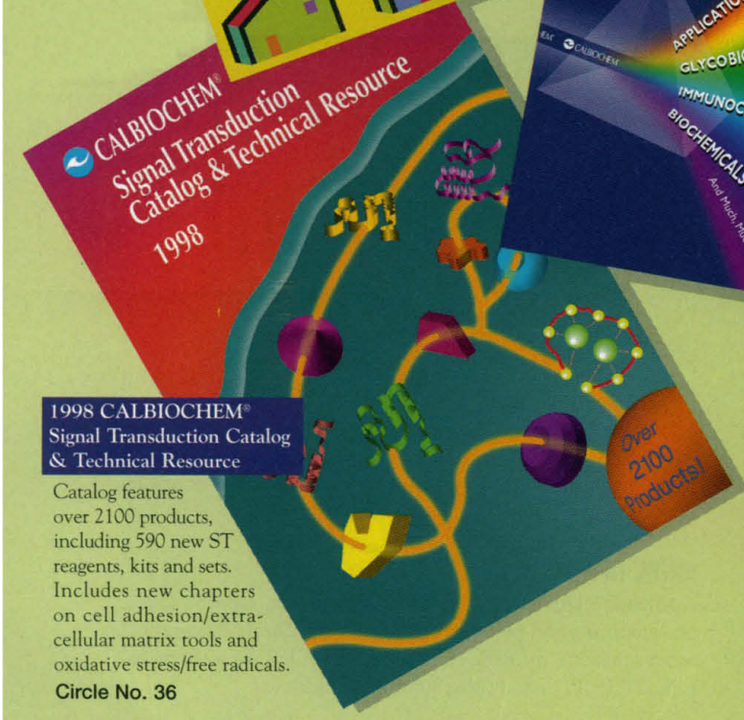

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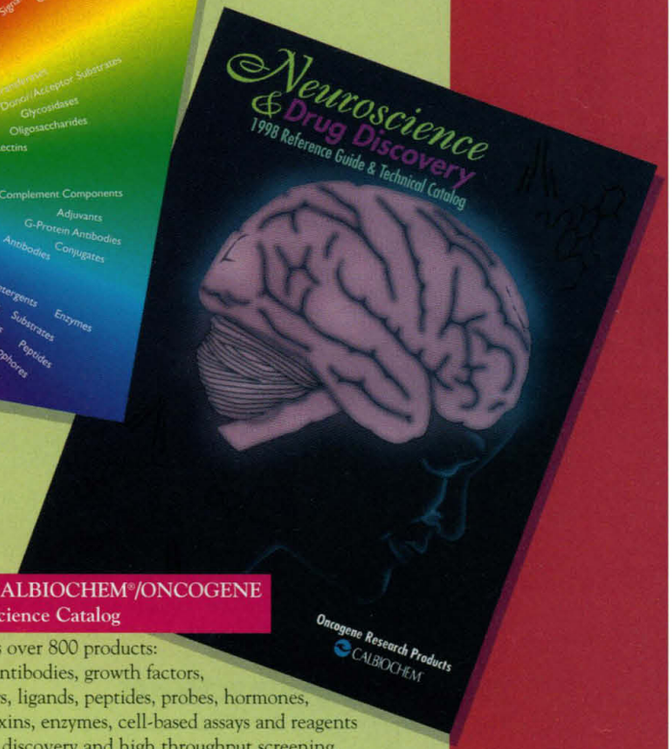

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