24 May 2002

Science

Vol. 296 No. 5572
Pages 1353–1556 $9

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

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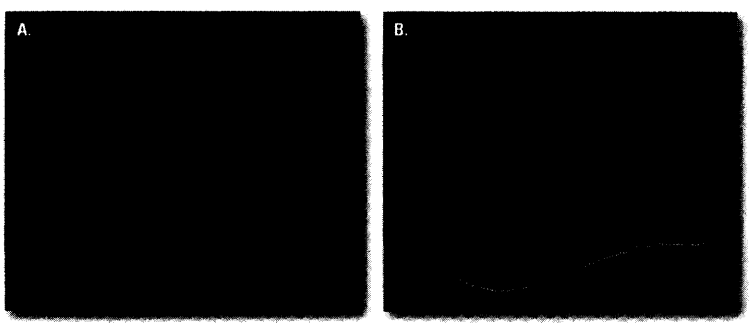

RNAi in *C. elegans*
Fluorescence microscopy of a *C. elegans* adult female with a transgenic GFP reporter gene (green) highly expressed in the pharynx (A). Double-stranded RNA corresponding to the GFP coding region was produced using the HiScribe RNAi Transcription Kit and injected into the syncytial gonad of transgenic adult worms. RNAi is demonstrated by the reduction of GFP expression in the progeny (B).

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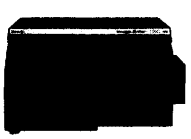
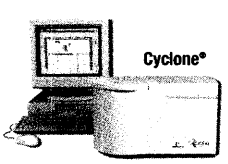


DNA Thunder



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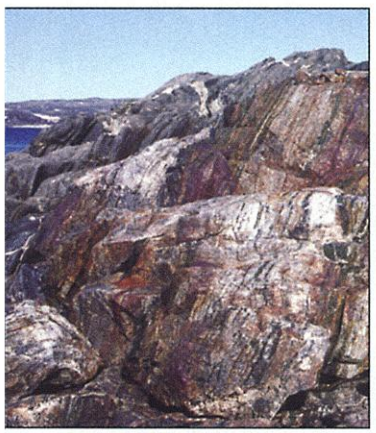
Science

Volume 296 24 May 2002 Number 5572

NEWS



1384
Contested glimpses of early life

NEWS OF THE WEEK

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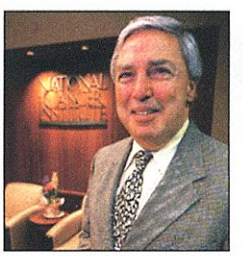
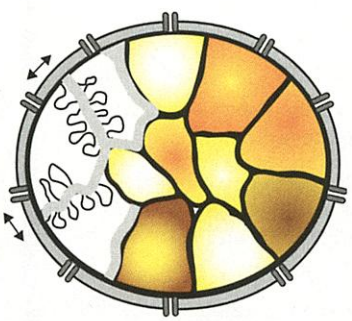
Profile of NCI's new chief



SCIENCE'S COMPASS



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Chromosomes in motion

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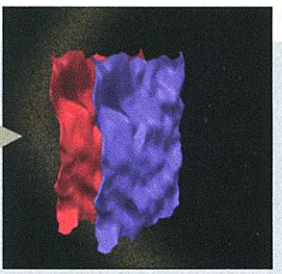
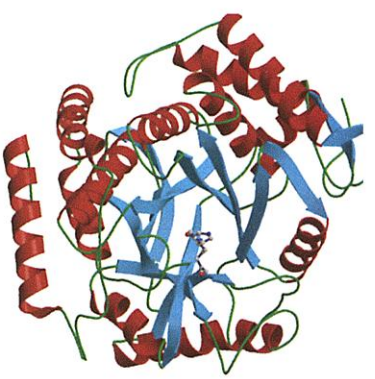


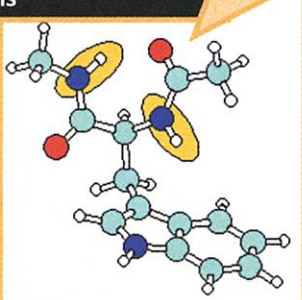
1417

In a new "cyclic" model, the Universe consists of two infinite three-dimensional membranes ("branes") that collide and bounce apart every few trillion years (counterclockwise). Our visible world corresponds to the left brane in each frame. Each collision yields new matter and radiation, which cool to form new galaxies and stars. After trillions of years of accelerated expansion, the Universe becomes empty and the cycle begins anew. More information on branes and other multidimensional concepts can be found in the special section in this issue. [Image: J. Mazeika and P. Steinhardt]



1462 Amino acid number 22

New on *Science* Express Propelling peptide contortions



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CONTENT HIGHLIGHTS AS OF 24 MAY 2002

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Conformational Dynamics in a Dipeptide After Single-Mode Vibrational Excitation B. C. Dian, A. Longarte, T. S. Zwier

Three distinct conformations of a methyl-capped dipeptide can be interconverted in the gas phase by exciting specific vibrations with infrared radiation.

An Alternative Flavin-Dependent Mechanism for Thymidylate Synthesis H. Myllykallio *et al.*

PERSPECTIVE: **DNA Building Block Re-Invented** A. G. Murzin

A distinct class of thymidylate synthase occurs in microbial genomes that lack the classical synthase, including several human pathogens.

The Structure of Haplotype Blocks in the Human Genome

▼ S. B. Gabriel *et al.*

1391 A genome-wide survey of patterns of single nucleotide polymorphisms in four population groups reveals that the human genome can be divided into blocks.

TECHNICAL COMMENTS

Calculating Forest Biomass Changes in China

Fang *et al.* (Reports, 22 June 2001, p. 2320), using historical forest inventory records, calculated that forest biomass storage of carbon in China had increased significantly since the mid-1970s, "mainly due to forest expansion and regrowth." Zhang and Xu comment that "the equation used to estimate forest biomass" by Zhang *et al.* "is questionable," because it purportedly relies on site classification data that "have not been available in any Forest Resource Statistics of China since the 1950s." Fang *et al.*, in their response, show that the expression cited in the original paper is "mathematically equivalent" to a simpler expression that does not depend on site class information.

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/296/5572/1359a

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CANADA: **Drawing Body Parts for a Living** M. Guilderson

Medical illustrators operate at the intersection of art and science.

U.S.: **When a Mentor Becomes a Thief** C. Woolston

In some labs, it's routine to steal other people's work.

U.K.: **Big Opportunities in a Nano World** J. Wilkins

Nanobiotechnology, a priority area for the BBSRC, offers good job prospects.

EUROPE: **Web Sites to Watch—The Joint Research Centre** K. Urquhart

The JRC, which provides support for European policy-makers, is looking for Ph.D. and postdoctoral fellows.

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Provoking Rage I. Chen

Protein fans the flames of cranky joints.

Genes, Culture, and Aging Flies—What the Lab Can and Cannot Tell Us About Natural Genetic Variation for Senescence C. C. Spencer and D. E. L. Promislow

Laboratory techniques might skew our view of aging.

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signal transduction knowledge environment

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Perspective: Paradigms of Growth Control—Relation to Cdk Activation N. Olashaw and W. J. Pledger

How growth factors and cell density conditions signal to cyclin-dependent kinases to control cell proliferation.

Connections Maps: $G\alpha_{12}$ and $G\alpha_{13}$ Pathways Pathway Authorities: S. Neves, P. Ram, R. Iyengar

Explore the G protein signaling pathways used by the most abundant growth factor in serum and a key mediator of asthma.

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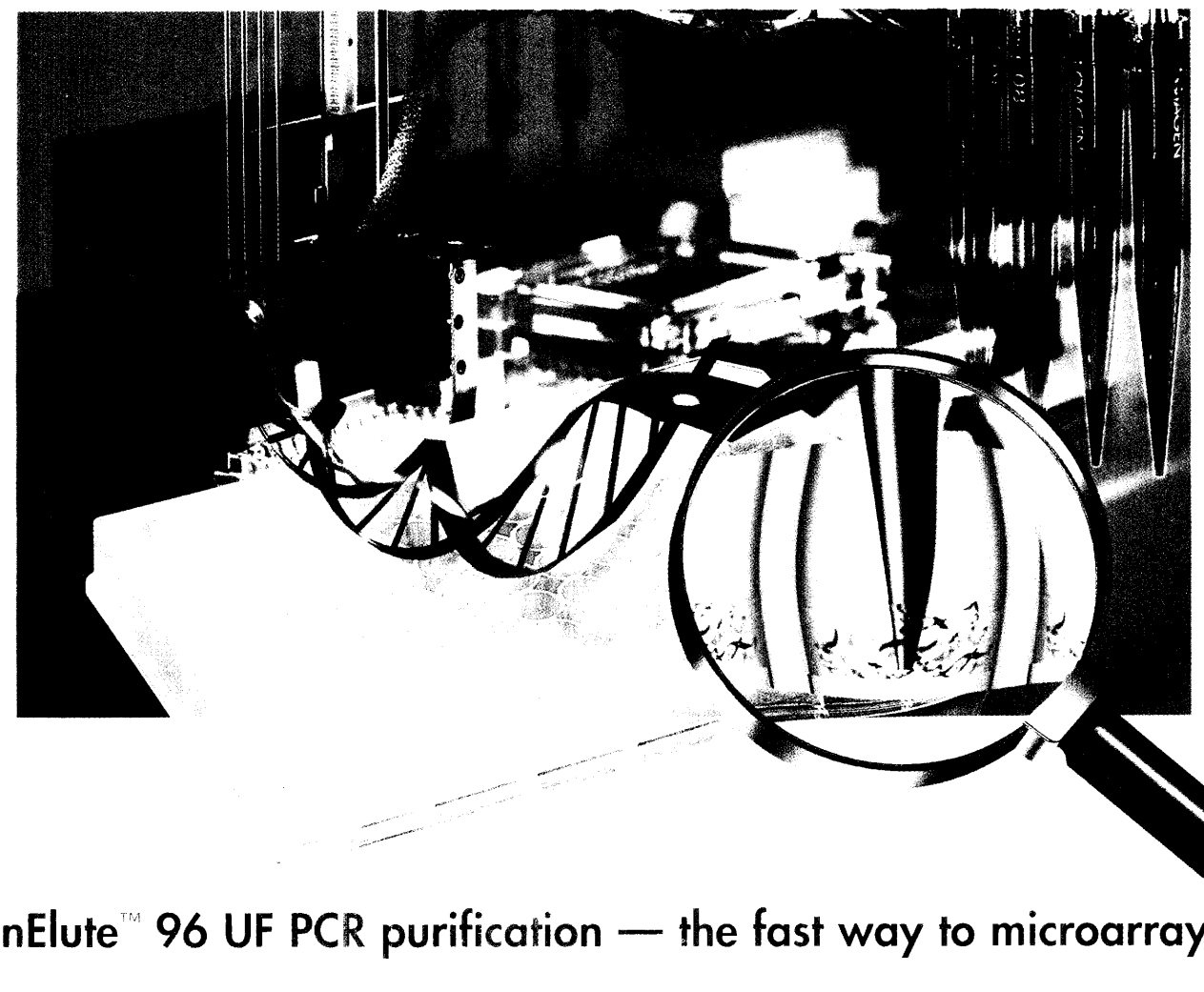

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THIS WEEK IN Science

edited by Phil Szuromi

Traces of Monkey Business

To what degree do chimpanzees use tools, and how might their use look in an archaeological context? Mercader *et al.* (p. 1452; see the news story by Vogel) describe an excavation of a chimpanzee nut-cracking site, in which chimpanzees evidently collected useful stones and transported them to the site. The site shows a large number of flaked and broken stones that may superficially resemble aspects of early hominid sites.

Cyclic Universe

The standard model of the origin of the universe begins with the big bang, which was followed by a period of inflation, a brief period of rapid expansion of spacetime. Steinhardt and Turok (p. 1436) have revived an old theory by proposing a new model that has no beginning or end, but is composed of a series of bangs (explosive expansions) and crunches (contractions). They use a negative potential energy, which is motivated by string theory, rather than spatial curvature to cause the reversals from expansion to contraction. Unlike the standard model, the cyclic universe can explain the recent discoveries of accelerated expansion and dark energy. ✗

The Great Escape

The hypothesis that human immunodeficiency virus–type 1 (HIV-1) mutates in order to "escape" recognition by cytotoxic T cells (CTL) has endured for over a decade without direct evidence to support it. Moore *et al.* (p. 1439; see the Perspective by McMichael and Klenerman) searched at a population level for selection of HIV-1 variants within a sequence corresponding to 207 amino acids of the viral reverse transcriptase gene. In an extensive cohort of HLA allele–typed individuals, polymorphisms in or around CTL epitopes covered by the consensus sequence were significantly associated with high viral load. Evasion of HIV-1 from the CTL radar screen will be a critical consideration in HIV-1 vaccine and therapy design.

Unpredictable Wiring Diagrams

Making predictions of the behavior of genetic networks may be even more complicatd than previously thought. Guet *et al.* (p. 1466; see the Perspective by Wigler and Mishra) created libraries of synthetic genetic networks in *Escherichia coli*. LacI, TetR, and lambda CI, along with five promoters regulated by these proteins, were linked together in various orders on plasmids. Two chemical inducers that change the binding state of LacI and TetR were used as inputs, and a fluorescent reporter of activity was used as the output. There were surprises even within such well-characterized components. A single swap of the connections between promoter and DNA binding protein could dramatically change the behavior of the network.

1443

Multitasking Molecules

An organic molecular conductor based on a spiro-biphenalenyl neutral radical can simultaneously exhibit bistable electrical, optical, and magnetic states that arise through internal charge transfer. Itkis *et al.* (p. 1443) show that in the high-temperature paramagnetic form, the unpaired electrons are separated on the exterior phenalenyl units of a dimer unit. In the spin-paired low-temperature diamagnetic state, the electrons migrate to the interior phenalenyl units and spin pair as π-dimer. The paramagnetic state is electrically insulating and transparent in the infrared, whereas the diamagnetic state is conducting and opaque in the infrared.

And in Brevia ...

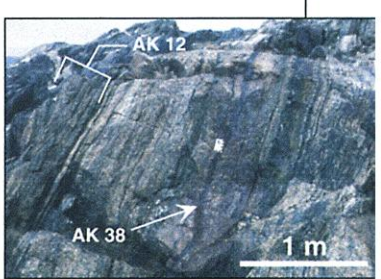
Critical differences in speech that occur when people talk to pets rather than to babies are described by Burnham *et al.* (p. 1435).

Signaling Shortcut

The yeast mating response to pheromones involves transmission of signals through a cascade that begins at a cell surface pheromone receptor, couples to a heterotrimeric GTP-binding protein (G protein), and eventually activates a mitogen-activated protein kinase (MAPK). Metodiev *et al.* (p. 1483) report that the subsequent adaptation response to pheromones relies on this same general pathway but uses a shortcut. The Gα subunit of the G protein interacts directly with the downstream MAPK to down-regulate the mating signal. This strategy of circumvention may be applicable to other G protein–stimulated MAPK cascades in higher eukaryotes.

Life Signs Lost in Igneous Rocks

Pinpointing when life began on Earth has been difficult. The oldest fossils have been thought to be in rocks dated to 3.45 billion years ago, but recent results have questioned the biological origin of the purported fossils. Chemical evidence for older life has been presented based on carbon isotope signatures in ancient rocks in Greenland. The oldest signature has been reported to be preserved in graphite inclusions in apatite crystals in metamorphic rocks on the Island of Akilia thought to 3.8 billion years old. These graphite inclusions were interpreted as representing organic matter deposited with the rocks, which were thought to be sedimentary iron formations. Fedo and Whitehouse (p. 1448; see the news story by Kerr) now argue that the host rocks are actually igneous rocks that were subsequently altered to form prominent banding. Any organic matter would not be primary in origin.



CREDIT: FEDO AND WHITEHOUSE

Preparing to Make the Cut

The hairpin ribozyme cleaves its substrate with heterogenous reaction kinetics. Now Zhuang *et al* (p. 1473) have used single-molecule fluorescence methods to show that this heterogeneity in function is linked to complex structural dynamics. The ribozyme exists either in an undocked conformation or in one of four distinct docked states. Individual molecules exhibit a "memory effect" and rarely switch between different docked states. Cleavage only occurs in the docked state, and the combination of multiple undocking rates and the mem-

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CONTINUED ON PAGE 1363

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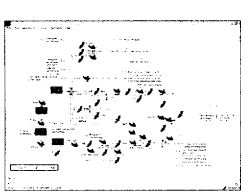

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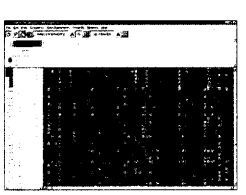
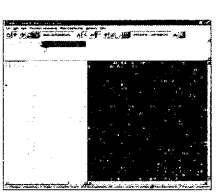


CLASS PREDICTION ALGORITHMS (BAYESIAN CLASSIFIERS). Incorporate prior knowledge into your analysis to classify data. Predict the phenotype or class of an unknown sample.



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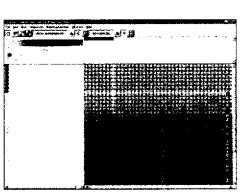
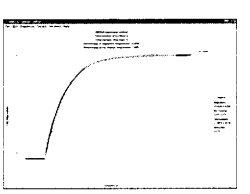


PATTERN DISCOVERY (GROW ALGORITHM). Identify patterns by specifying several genes or experiments of interest. These specified items are averaged into a "virtual gene" or a "virtual experiment" and used in similarity searches against stored data to discover patterns.



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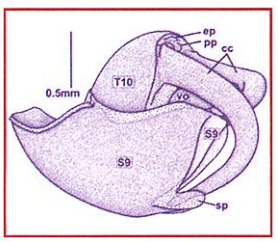
ory effect explains the heterogenous cleavage reaction kinetics. Complex structural dynamics linked to function is likely a general feature of RNA kinetics.

Learning in Adults and Children

One of the challenges in studying the development of cognitive functions in humans is the expectation that both anatomical and functional components of the brain are developing, not merely during infancy but well into adolescence and perhaps even adulthood. Schlaggar *et al.* (p. 1476; see the Perspective by Casey) provide a behavioral and brain imaging study in which they describe a new approach for parsing age-related and performance-related developmental events. They assess how children (ages 7 to 10) and adults generate words in a lexical processing task, and they find that adults utilize a left dorsal frontal region, while children apparently do not have functional access to this region and rely on an extrastriate area. One explanation is that this alternative strategy is discarded as frontal functions mature.

Whither Thou Goest...

In addition to the generation of movements, the brain must also create an internal record providing information about impending movements. Information about upcoming movements is generated by creating a correlate, or corollary discharge, of the neuronal activity that commands movement. Sommer and Wurtz (p. 1480) provide evidence for correlate formation in the case in a previously identified pathway from brainstem to frontal lobe. Corollary discharge signals emanating from the superior colliculus are relayed through the mediodorsal nucleus of the thalamus upstream toward the frontal eye field. The prefrontal areas will be informed through this pathway of collicular neuronal activity associated with the generation of ocular saccades.



A New Order

Almost a century has elapsed since a newly described insect has proved unplaceable within a recognized order—major groupings, such as beetles and flies. Now, Klass *et al.* (p. 1456: see the 19 April news story by Pennisi) announce the discovery of a new extant insect taxon: The new order, Mantophasmatodea, appears to be related to Phasmatodea (stick insects), and is described on the basis of two museum specimens from Namibia and Tanzania. The authors also note the occurrence of Mantophasmatodea in Baltic amber, which demonstrates a much wider geographical distribution of the group in the Tertiary.

Adding Pyrrolysine to the Code Book

In 1986, selenocysteine was identified as the 21st amino acid when it was found to be directly encoded by UGA, which usually specifies translation termination. Now two reports show that amber codons in the methyltransferase genes of certain archaea encode a novel lysine derivative (see the Perspective by Atkins and Gesteland). Hao *et al.* (p. 1462) provide crystallographic evidence that UAG is decoded as pyrrolysine, and Srinivasan *et al.* (p. 1459) characterize a specialized transfer RNA (tRNA) that can be charged with lysine by an unusual tRNA synthetase. By analogy with the selenocysteine translation mechanism, it is likely that the tRNA is charged with lysine and is then modified to pyrrolysine before UAG is decoded.

A Clue to Cachexia

Patients with chronic diseases such as cancer and AIDS often develop cachexia, a life-threatening disorder characterized by extensive weight loss and degeneration of skeletal muscle. The molecular pathogenesis of cachexia is poorly understood. Zimmers *et al.* (p. 1486) show that mice develop a wasting syndrome resembling human cachexia when they are systemically administered high levels of myostatin, a member of the transforming growth factor–β family. Prior administration of proteins that inhibit myostatin activity, such as follistatin, slowed weight loss in the mice. These results suggest that myostatin may be a useful drug target for prevention or treatment of cachexia, which is estimated to be the ultimate cause of death in about 25% of all cancer patients.

CREDIT: KLASS *ET AL.*

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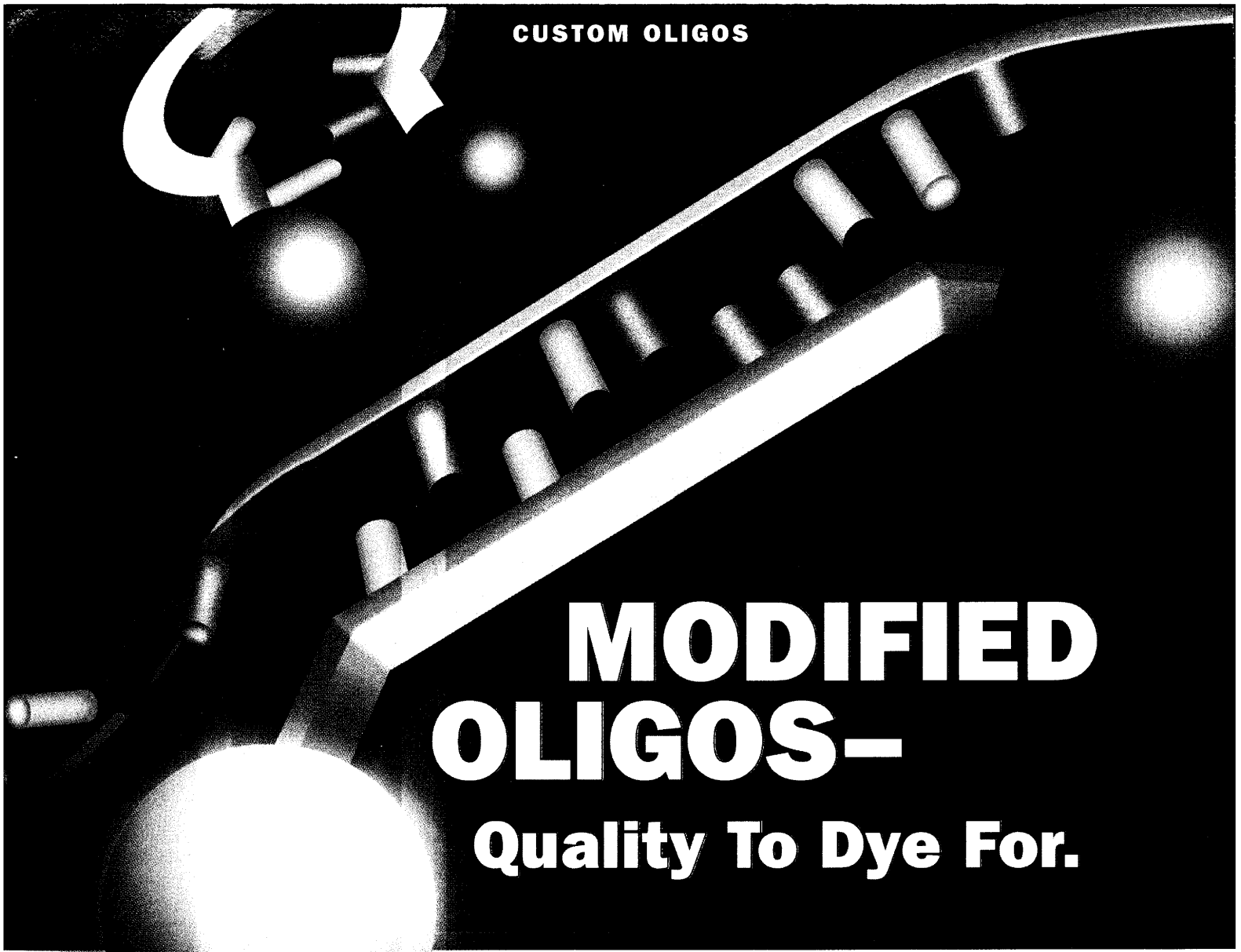

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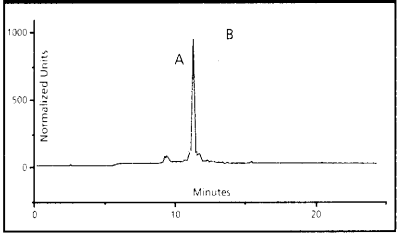

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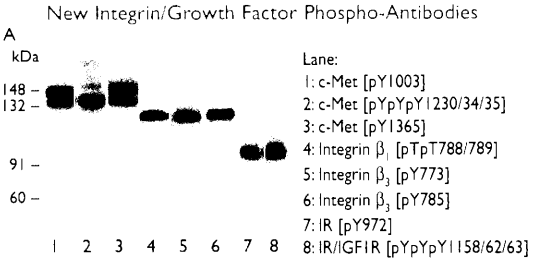

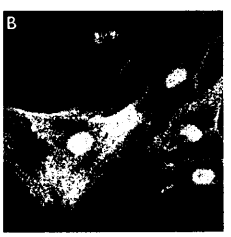

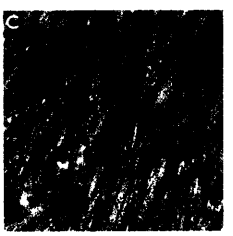

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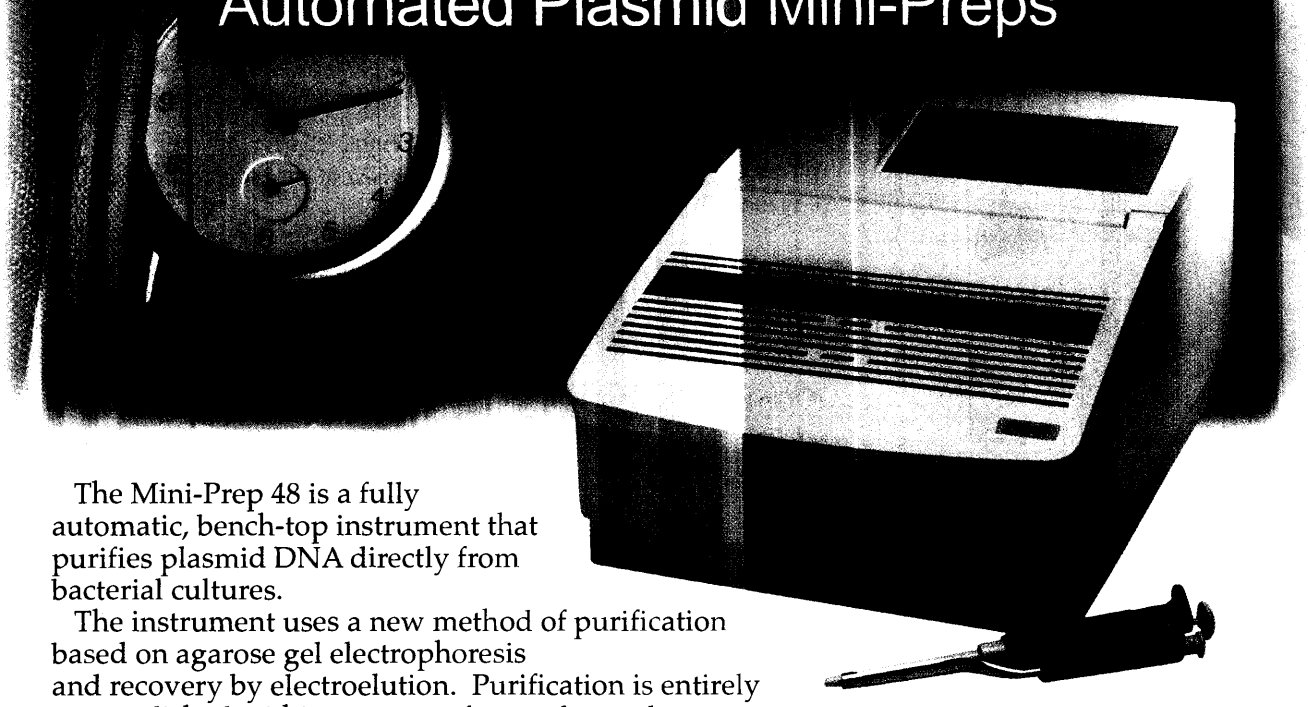

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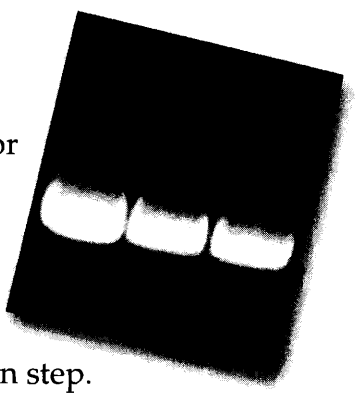

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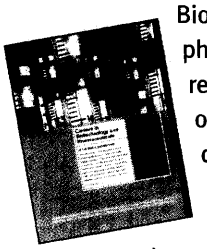

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Go to **www.amershamscienceprize.org** to obtain the mandatory entry form. And take your step. Jamie H. Cate did and won the regional prize for North America in 1998. What's more, he recently won a prize for the best paper published in *Science*—"Crystal Structure of the Ribosome at 5.5 Å Resolution" *Science*, **292**: 883-896 (2001).

* For the purpose of this prize, molecular biology is defined as "that part of biology which attempts to interpret biological events in terms of the physico-chemical properties of molecules in a cell" (McGraw-Hill Dictionary of Scientific and Technical Terms, 4th Edition).

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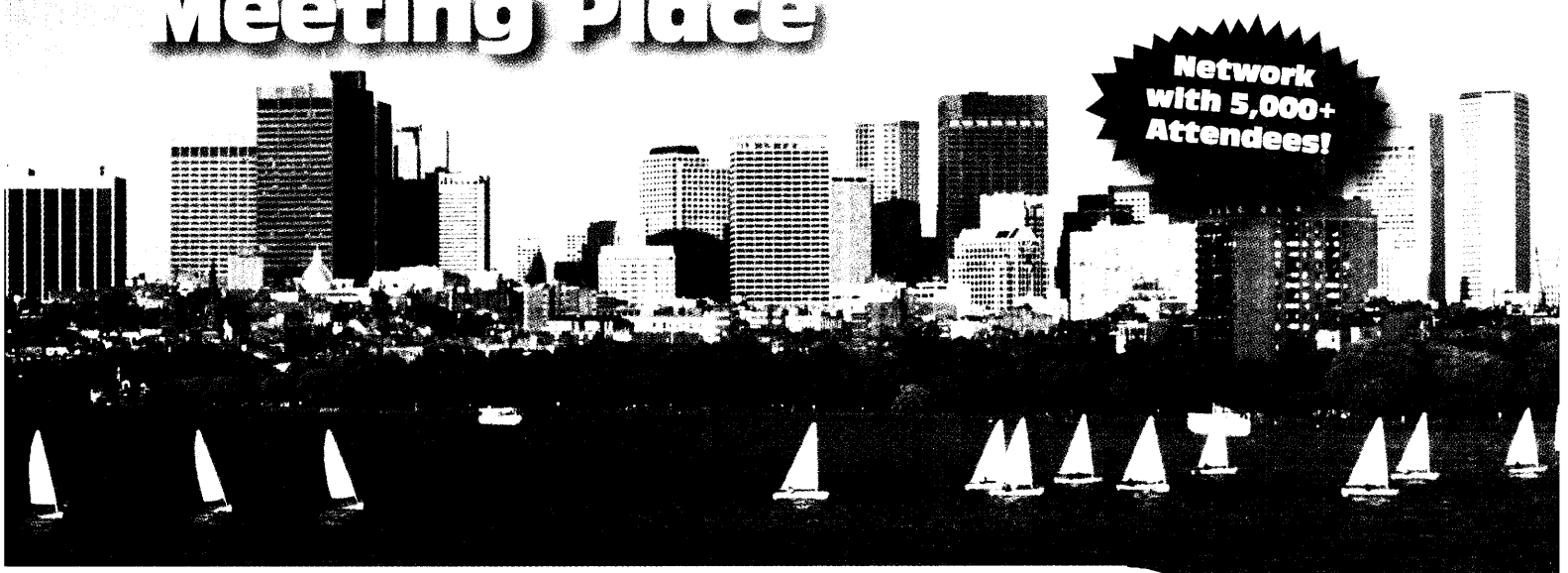

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FAMRI ANNOUNCES THE SECOND YEAR CLINICAL RESEARCH AWARDS

In October 1991, Miami attorneys, Stanley and Susan Rosenblatt, brought a class action suit against the tobacco industry seeking damages on behalf of flight attendants and their survivors, for the diseases and death that have been caused by their exposure to secondhand tobacco smoke in airline cabins. The October 1997 settlement, after four months of trial, among other substantial benefits to class members, established an endowment fund of $300 million that has supported a not-for-profit research foundation, the Flight Attendant Medical Research Institute (FAMRI). The Mission of FAMRI is to sponsor scientific and medical research for the early detection, treatment, and cure of diseases and medical conditions associated with exposure to secondhand tobacco smoke. FAMRI is governed by a Board of Trustees with the majority of flight attendants. A Medical Advisory Board of highly qualified, internationally recognized clinical scientists, chaired by former United States Surgeon General Julius Richmond, M.D, and a Lay Advisory Board of dedicated concerned citizens assist the Governing Board in decision-making. FAMRI has contracted the American Institute of Biological Sciences to conduct the peer review of proposals for the three clinical research awards detailed below. More information about FAMRI and the awards, including the Requests for Applications will be available on the web at: http://www.famri.org after May 1, 2002. Other communications and queries should be directed to: Beth Kress, FAMRI Executive Director, 201 S. Biscayne Blvd., Suite 1310, Miami, FL 33131. E-mail famri@bellsouth.net; phone, 305-379-7007; fax, 305-577-0005.

YOUNG CLINICAL SCIENTIST AWARD (YCSA)

The purpose of the FAMRI YCSA is to help prepare and support new clinical investigators with a M.D. or Ph.D. as they begin their careers as independent researchers. The program is limited to the development of young researchers in smoking-related disorders. FAMRI is particularly interested in helping to provide the bridge between the clinic and the laboratory for the critical translation of basic research findings into diagnostic and therapeutic approaches. The YCSAs are being offered to two groups of scientists: research fellows and junior faculty members.

CLINICAL INNOVATOR AWARD (CIA)

FAMRI established the CIA to stimulate novel medical and clinical scientific research studies on the effects of exposure to secondhand tobacco smoke. While considerable government and non-government funding is available to support established mainstream biomedical research projects, funds for high-risk projects are generally quite limited. With the CIA, FAMRI hopes to foster innovative breakthroughs and creative collaborations. The CIA is available to clinical investigators with a M.D. or Ph.D.

CENTER OF EXCELLENCE (CoE)

FAMRI's CoE will be the centerpiece to linking physicians and scientists from various discipl multidisciplinary programs in patient care and research. The aims of FAMRI's Centers of Excellence are to enhance the knowledge base relating to exposure to second hand tobacco smoke, to serve as a new source for more effective approaches to detection, diagnosis, and therapy for diseases associated with such exposure, and to serve as principal deliverers of medical advances to those suffering from such exposure, especially flight attendants. FAMRI has developed this award program on an institutional basis, striving for comprehensive research plans, including the entire range of research endeavors from basic to clinical research, as well as community outreach.

FAMRI does not support individuals who
or institutions that are currently receiving funds from the tobacco industry or its affiliates.
Full disclosure of any prior tobacco industry funding is required of all applicants.

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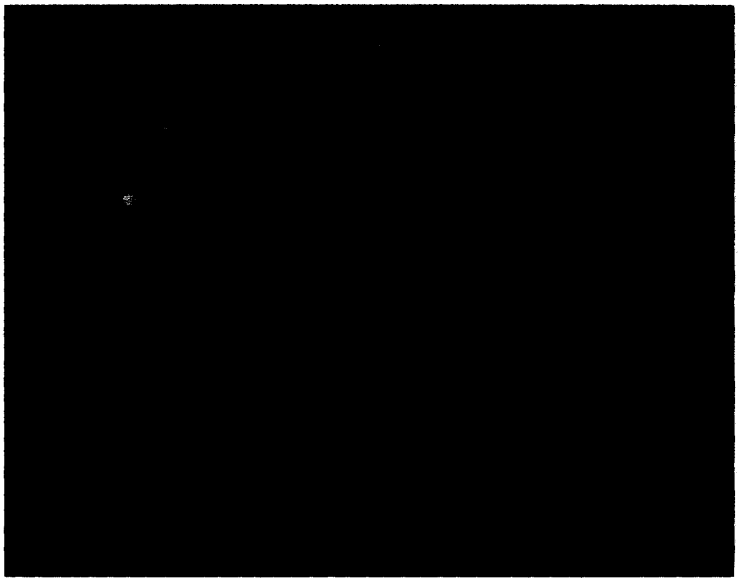

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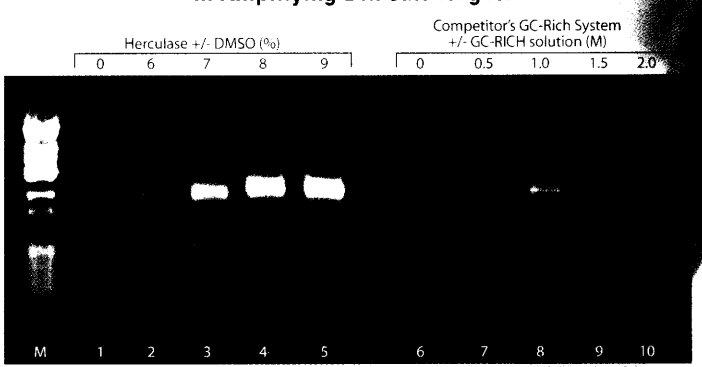

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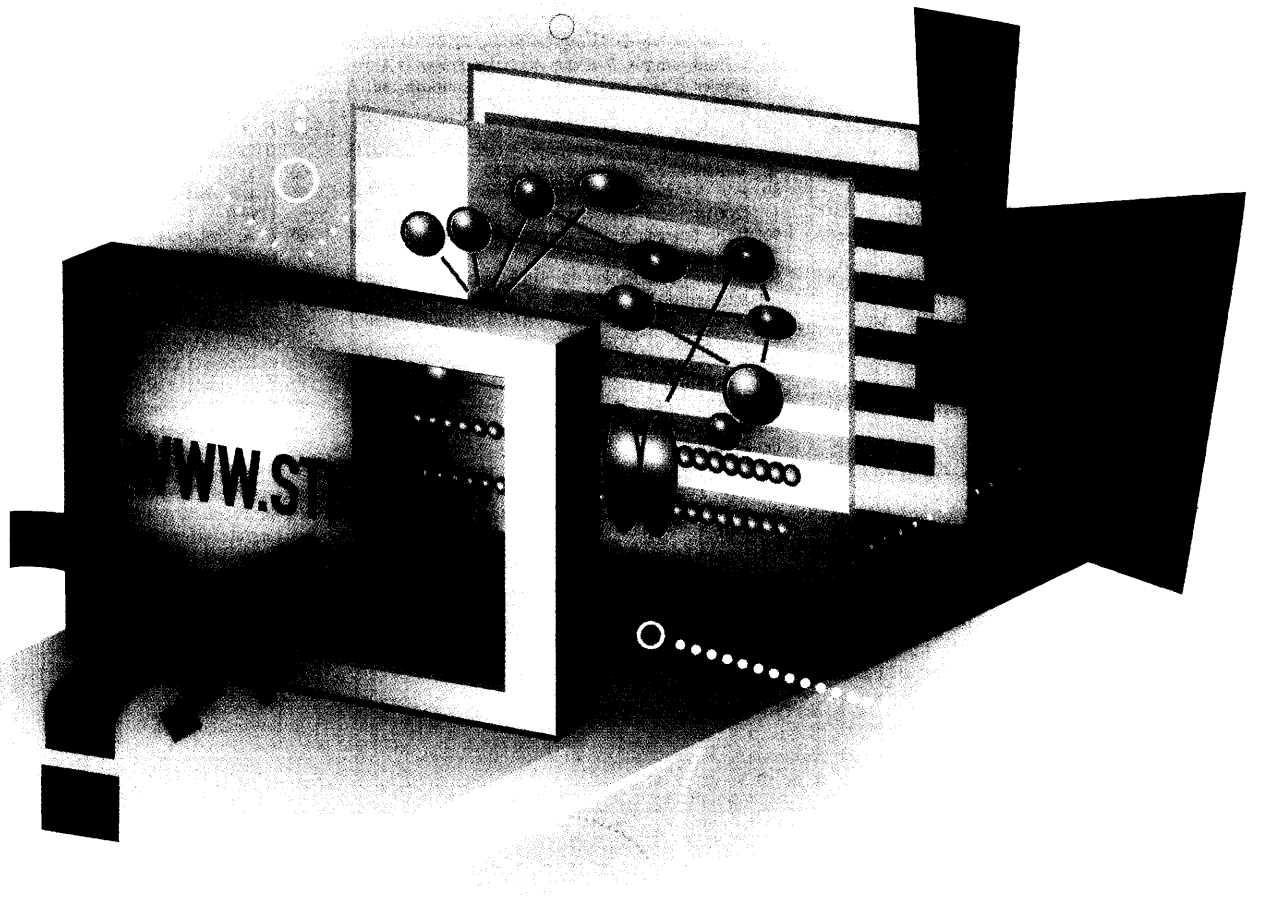

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