

The background of the cover is a complex, abstract design. It features a blue-toned grid of squares, overlaid with a network of glowing white and light blue lines that resemble circuit traces or neural pathways. These lines intersect and branch out across the frame. In the center-right, there is a bright, glowing sphere. A green, ribbon-like helix, similar to a DNA double helix, is wrapped around the sphere. The overall aesthetic is high-tech and scientific, with a color palette dominated by blues, whites, and a touch of green.

# Science

31 May 2002

Vol. 296 No. 5573  
Pages 1557-1752 \$9

## Mapping Cellular Signaling



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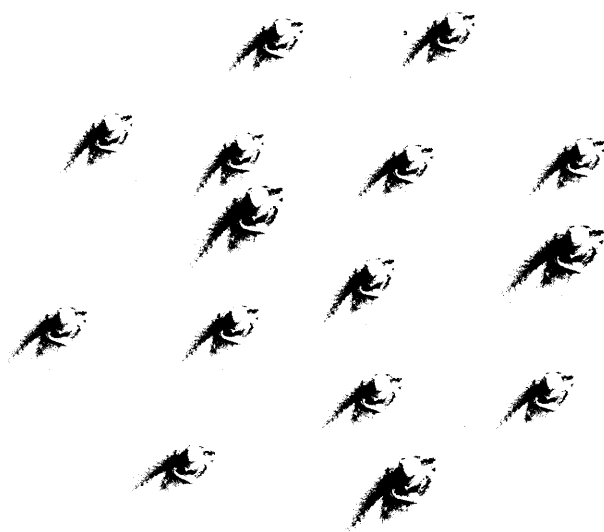
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## NEWS

1592

Smallpox scenarios



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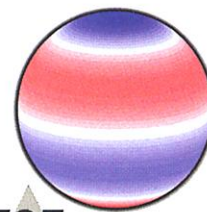
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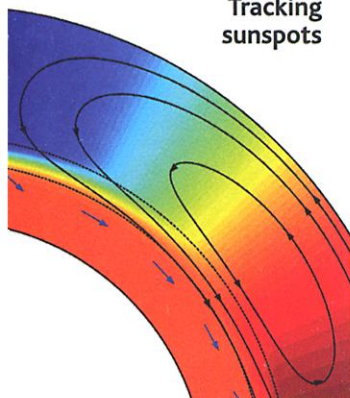


1617

Seeing ourselves in a mouse chromosome

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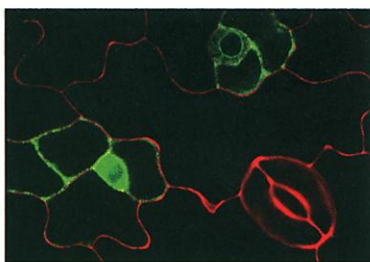
Tracking sunspots





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Too many  
mouths in  
*Arabidopsis*



## MAPPING CELLULAR SIGNALING

In this joint special issue, *Science* magazine and *Science's STKE* feature coordinated roadmaps to cellular signaling. The Viewpoints in this issue and related Connections Maps at *Science's STKE* (shown in blue below) highlight physiological control mechanisms from immunology, neurobiology, cell biology, developmental biology, and plant biology and reveal the intricate molecular mechanisms by which cells respond and adapt to their environment. [Image: Julie White]



**COVER 1632**

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- 1655 **The Phosphoinositide 3-Kinase Pathway** L. C. Cantley **PHOSPHOINOSITIDE 3-KINASE PATHWAY**

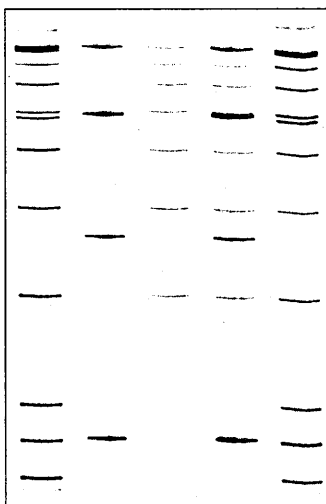
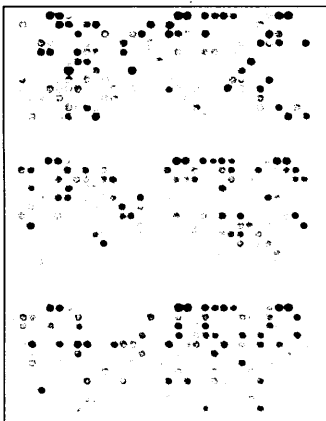
## New on Science Express News from Mars Odyssey



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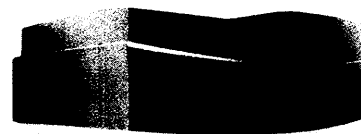
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CONTENT HIGHLIGHTS AS OF 31 MAY 2002

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### SCIENCE EXPRESS

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**Distribution of Hydrogen in the Near-Surface of Mars: Evidence for Subsurface Ice Deposits** W. V. Boynton *et al.*

**Global Distribution of Neutrons from Mars: Results from Mars Odyssey** W. C. Feldman *et al.*

**Maps of Subsurface Hydrogen from the High-Energy Neutron Detector, Mars Odyssey** I. Mitrofanov *et al.*

**PERSPECTIVE: Tip of the Martian Iceberg?** J. Bell

Mapping of secondary neutron and gamma ray fluxes from the martian surface by three Mars Odyssey spectrometers suggests a subsurface rich in frozen water, from the edge of the polar caps to the midlatitudes.

**Requirement for Hippocampal CA3 NMDA Receptors in Associative Memory Recall** K. Nakazawa *et al.*

In mice, elimination of one kind of synapse in the brain impairs the ability to recall the location of a hidden platform when given limited clues.

## TECHNICAL COMMENTS

### Groundwater Flow in the Ganges Delta

Basu *et al.* (Reports, 24 August 2001, p. 1470) reported that groundwater flow in the area of the Ganges-Brahmaputra (G-B) river delta represents "a potentially significant source of strontium to the oceans, equal in magnitude to the dissolved strontium concentration carried to the oceans by the G-B river waters," a finding with potentially significant implications for interpretation of the marine strontium isotope record. Harvey, in a comment, argues that "the large estimate of regional groundwater flow by Basu *et al.* is implausible given the extremely flat topography of the Ganges delta," and that the helium-tritium ratios used to establish the groundwater age and recharge rate "may reflect irrigation pumping rather than basin-scale flow." Basu *et al.* respond that the hydrologic issues raised by Harvey "are not central to the main conclusions of our study . . . on the marine Sr budget" and present additional data that they maintain argue strongly "against Harvey's contention of groundwater drawdown by irrigation pumping."

The full text of these comments can be seen at [www.sciencemag.org/cgi/content/full/296/5573/1563a](http://www.sciencemag.org/cgi/content/full/296/5573/1563a)

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**GERMANY: Biotechnology Is Still a Growth Industry**

E. von Ruschkowski

The 3rd Biotechnology Report indicates that biotech is still hot.

**US: Sharing in the Sciences—An Ethics Mini-Feature** Edited by K. Cottingham

Can academic scientists really share data and materials openly—and do they?

**CANADA: Project Management for Scientists, Part 1** M. Kashyap

Companies are crying out for project managers. Can scientists fill the niche?

**SINGAPORE: A Career in Medical Writing—A Singaporean's Perspective** Y. J. Ping

A firsthand account of medical writing in Singapore.

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### The Naked Mole-Rat—A New Record for the Oldest Living

Rodent R. Buffenstein and J. U. M. Jarvis

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# THIS WEEK IN Science

edited by Phil Szuromi

## Unsuspected Depths

Sunspots reveal open magnetic field line regions on the Sun that are directly related to the dynamo mechanism that creates the magnetic field structure. Observations indicate that most sunspots form at low latitudes, but models based on the measured solar rotation place sunspots at high latitudes. Nandy and Choudhuri (p. 1671) have developed a dynamo model that resolves the latitudinal discrepancy by adding a deep meridional flow of material. This previously unrecognized flow could have important implications for the dynamical and chemical evolution of stars like our Sun.

## Subduction Tremor

Volcanic tremor is a low-frequency, long-period, and nearly constant amplitude waveform detected by seismometers in volcanic regions; it usually is associated with the movement of fluid or magma in a narrow volcanic conduit. Using the recently deployed 600 seismometers of the high-sensitivity seismographic network (Hi-net), Obara (p. 1679; see the Perspective by Julian) has detected the characteristic waveform of volcanic tremor in southwest Japan, even though there are no volcanoes in this region. The tremors are located along the strike of the subducting Philippine Sea Plate and extend to a depth of as much as 45 kilometers. These tremors are probably associated with the movement of fluids in narrow fractures along the subduction zone and represent a new seismic phenomenon.

## Suture, Knot Thyself

Shape-memory materials can undergo deformation but then recover their original shape after being heated above some critical temperature. Lendlein and Langer (p. 1673) now show that a number of shape-memory biodegradable polymers can be used as self-closing sutures. The polymer fibers were first stretched to create a deformed state. The fibers were then loosely sewn and knotted around an incision. Heating to body temperature caused the fibers to shrink and tighten and thus close the wound. The composition of these two-component polymers can be adjusted to change the transition temperature and restore stress for different applications. ✕

## They've Got the Beat

Individual harmonic oscillators with different frequencies, whether heart pacemaker cells or members of an audience clapping, can synchronize if they are coupled strongly enough. Theory has long sug-

## 1661 Of Mice and Humans

Mural *et al.* (p. 1661) provide a first peek at the differences between mammalian species with their analysis of the sequence of mouse chromosome 16. Gene content and order were highly conserved when compared with blocks of sequence on six of the human chromosomes. Only 14 of the 731 predicted genes on chromosome 16 were specific to the mouse. As Copeland *et al.* describe in a Perspective, such comparisons will provide insights into evolution and gene function.

## And in Brevia ...

Dinosaur tracks discovered by Day *et al.* (p. 1659) indicate that large, titanosaur sauropods were present by the Middle Jurassic, about 163 million years ago, and that they traveled in herds with other sauropods.

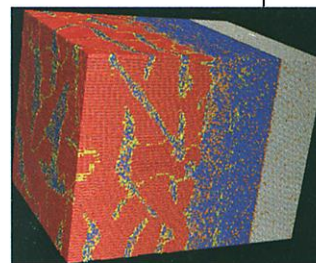
gested that a large number of oscillators should self-synchronize even with weak global couplings. Kiss *et al.* (p. 1676) studied a small set of noisy harmonic oscillators (64 electrochemical cells) and verify experimentally the key predictions of this theory, including the observation of a critical point in the coupling strength. They also show that chaotic and even anharmonic oscillators exhibit similar self-synchronization responses.

## Less Is Less, But More Efficient

Sustainable agriculture depends on successful recycling and maintenance of soil quality during farming. Compared to modern conventional farming, organic farming systems make greater use of nutrient recycling and associated insect and microbial communities. Mäder *et al.* (p. 1694; see the news story by Stokstad) have compared the dynamics of conventional and organic farming over a 21-year field trial in Europe. Although the yield from the organically farmed plots was somewhat less than that from conventionally farmed plots, the organically farmed plots were considerably less demanding of fertilizer and energy input.

## Shock Treatment

It has long been known that steel can be hardened by rapid cooling, which causes a diffusionless structural transition, called a martensitic transformation, that may be triggered either by temperature or by pressure changes. Experimental and theoretical studies of these transformations are complicated by the fact that they involve small displacements of many atoms. Kadau *et al.* (p. 1681) use massively parallel molecular dynamics simulations of millions of atoms to elucidate what happens during shock-induced structural phase transformations. The predicted behavior as a function of shock strength and crystallographic shock direction can be tested with ultrafast time-resolved laser-generated x-ray diffraction.



## Folk Medicine Meets Nuclear Receptors

The gum resin of the guggul tree *Commiphora mukul* has been used in Ayurvedic medicine since 600 BC to treat a wide variety of ailments, including obesity and lipid disorders. Although not well known in Western medicine, an extract of this resin (guggulipid) is clinically approved and widely used in India as a cholesterol-lowering agent. Urizar *et al.* (p. 1703) show that guggulsterone, the active agent in this extract, is a potent antagonist ligand for the nuclear



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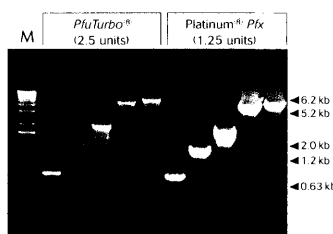
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hormone receptor FXR. As the primary bile acid sensor, FXR plays a central role in cholesterol metabolism; thus, this antagonist function is likely to be the molecular basis for guggulsterone's lipid lowering activity. These results raise the exciting possibility that FXR and other nuclear hormone receptors may mediate the effects of other biologically active natural products that could provide new leads for drug development. **X**

### Actions and Consequences

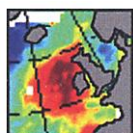
Our predictive understanding of the outside world is predominantly based on learning about the relationship between stimuli (classical or "Pavlovian" conditioning) and on learning about the consequences of our own behavior (operant conditioning). The neuronal mechanisms underlying operant conditioning are largely unknown. Brembs *et al.* (p. 1706; see the Perspective by Rankin) developed an operant conditioning paradigm in the marine invertebrate *Aplysia* and used in vivo and in vitro experiments to unravel the cellular basis of operant conditioning of feeding behavior.

### Warming Trend I: Boreal Forest Greening

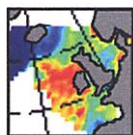
Satellite measurements have shown that the length of the growing season of high-latitude forests has been increasing over the past 20 years. This may be one of the first signs of an ecosystem response to global warming, but the observation alone does not explain which factors are responsible. Lucht *et al.* (p. 1687) employ a dynamic vegetation model and find that the main cause was the temperature increase during that period. The strength of the model is further demonstrated by its simulation of the decrease in vegetation that accompanied the cooling produced by the 1991 volcanic eruption of Mt. Pinatubo.

### Warming Trend II: Oxfordshire Flowering

Fitter and Fitter (p. 1689) have analyzed the flowering dates of 385 species of British plants over 47 years and shown: (i) that climate warming is having a powerful effect in advancing plant development, especially in the 1990s; (ii) that species differ greatly in their sensitivity to this warming, with spring-flowering, insect-pollinated species being most responsive; and (iii) that because of these large differences in response, there will be substantial ecological and evolutionary consequences, including changes in competitive interactions and in the probability of interspecific hybridization. The size of this data set allows a characterization of the nature and magnitude of the response in different plant species and life forms.



1960-1975



1992-1995

### Warming Trend III: North Atlantic Ecosystems

On the basis of marine plankton data gathered since 1946 in the Continuous Plankton Recorder survey, Beaugrand *et al.* (p. 1692) describe changes in the species composition of copepod biota in the North Atlantic during the past four decades. They find that southern species have migrated northwards in the eastern Atlantic along the coast of Europe, whereas northern or Arctic species have moved southwards in the western Atlantic off the coast of North America. These data are consistent with recent, anthropogenically mediated changes in climate, reflected by northern hemisphere temperature anomalies and the North Atlantic Oscillation.

### Are We There Yet?

During goal-directed activity, we continually update our current status with our expectations for finally attaining the goal. Expectation normally increases over the course of the activity, and, to find the neuronal signals that underlie this increasing expectation, Shidara and Richmond (p. 1709) analyzed single neuron activity in an area of the brain called the anterior cingulate cortex. They recorded from monkeys performing a sophisticated, multistep paradigm in which reward expectancy could be manipulated and found that in a subpopulation of neurons, activity was correlated with the expectation of reward. This study provides support for the important role of the anterior cingulate cortex in the representation of reward expectancy and emotional states, as discussed by Peoples in a Perspective.

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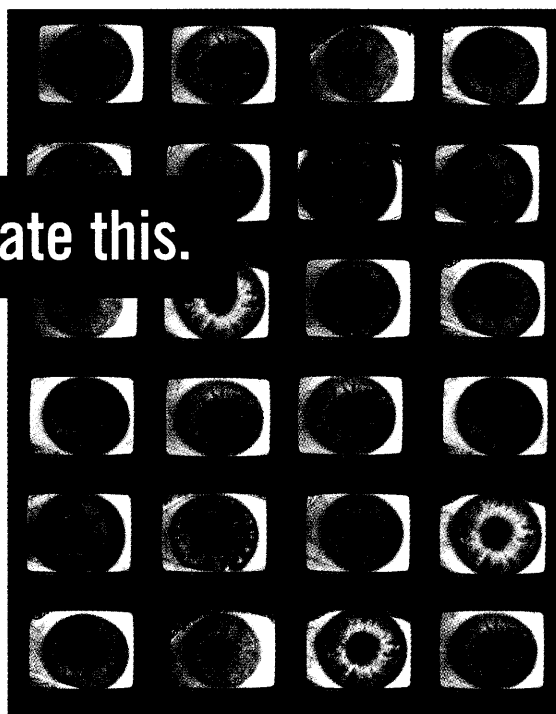
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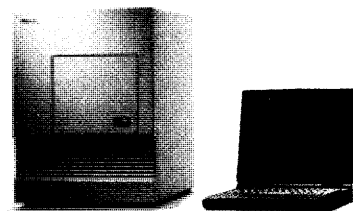
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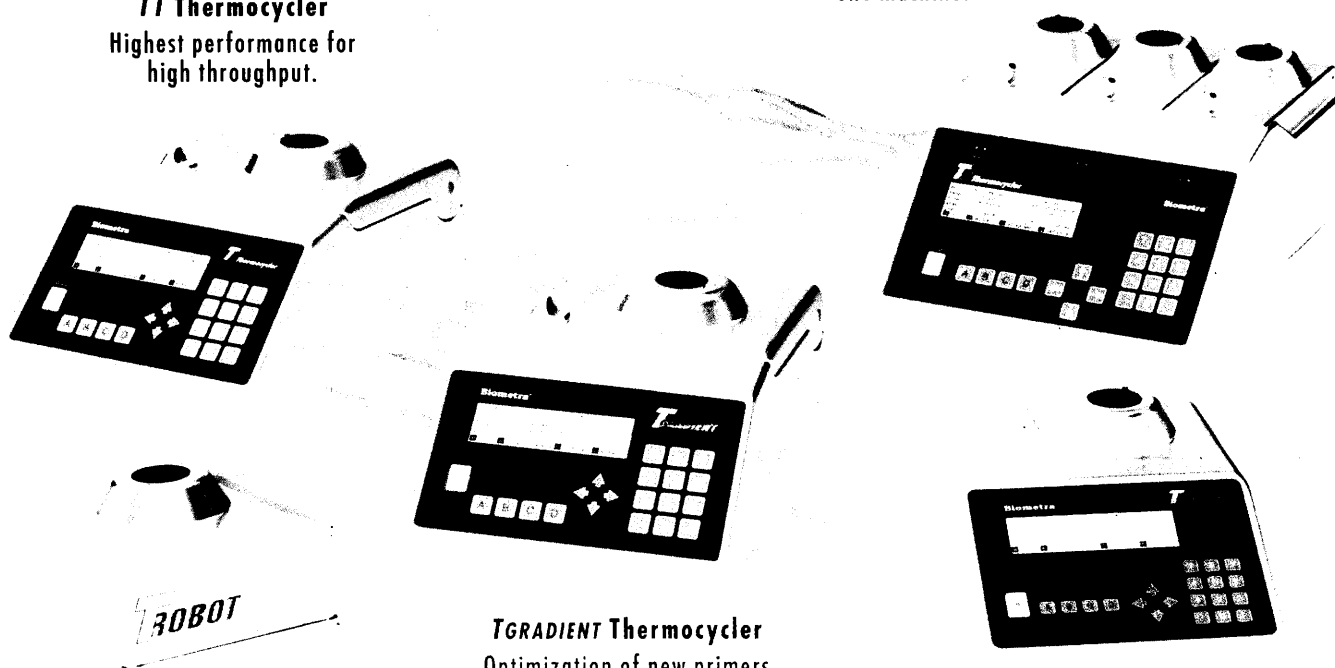
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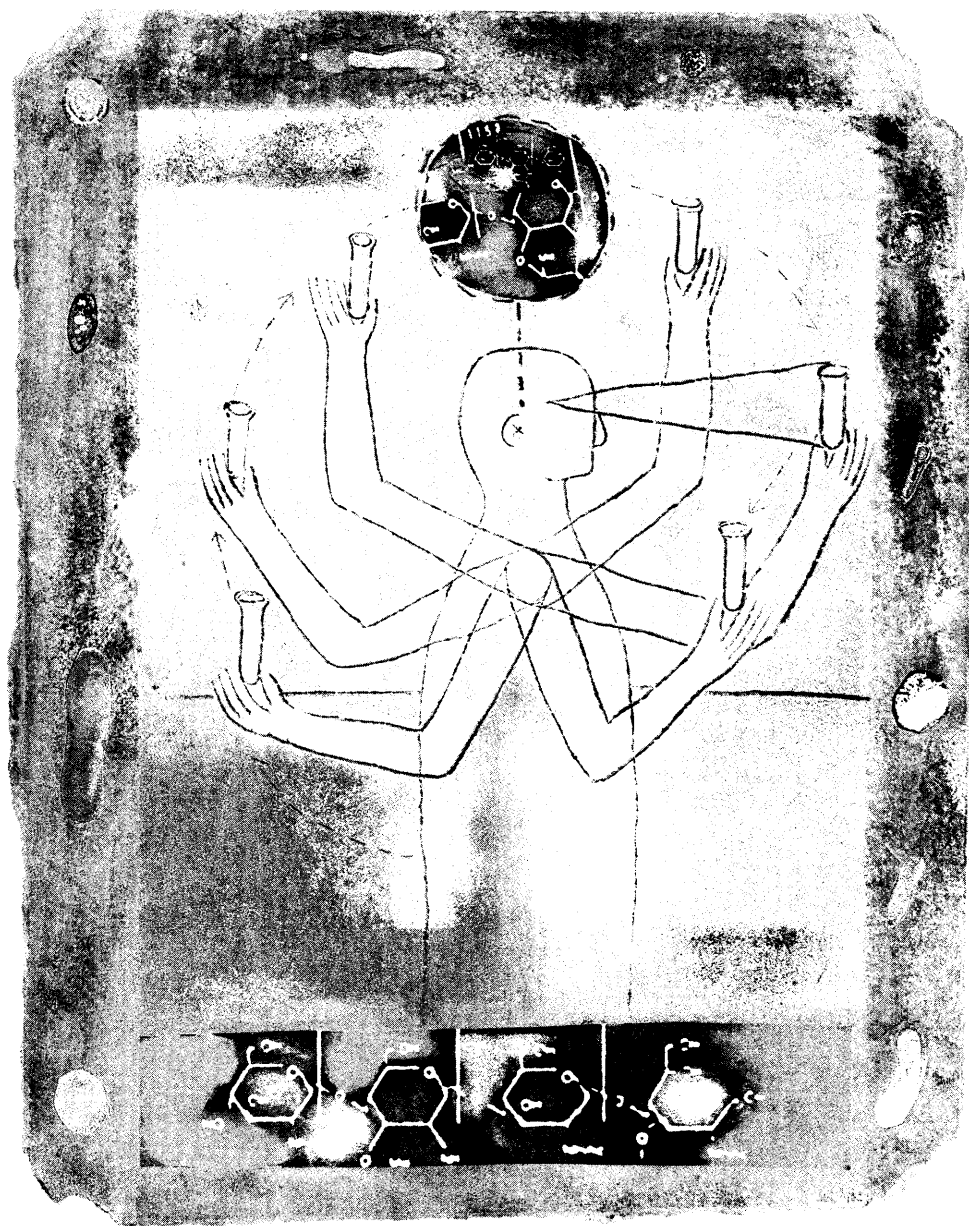
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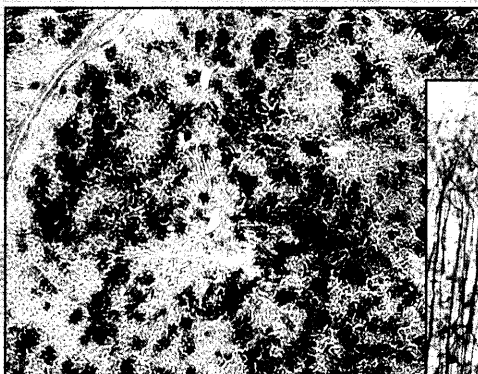
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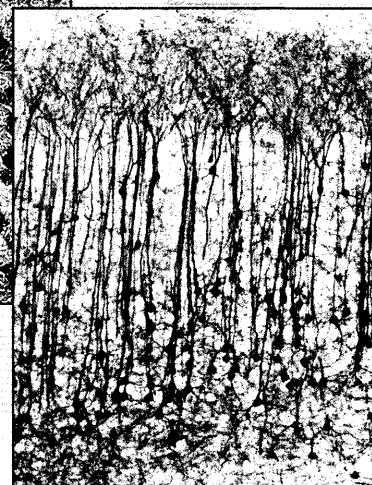


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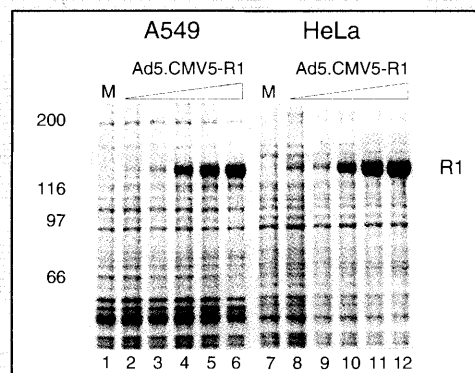


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- 1) Adult Balb/c mouse was injected in the retro-orbital vein with Ad5.CMV-LacZ. Courtesy of Andrea Amalfitano, Clinical Genetics, Duke University, Durham, North Carolina, USA.
- 2) Adult male Lewis rat was injected into the mid striatum with Ad5.CMV-HSV1tk. Cells illustrated are cortical pyramidal neurons retrogradely labeled from the injection site. Courtesy of Adam Zermansky, Maria G. Castro and Pedro R. Lowenstein, Gene Therapeutics Research Institute, Cedars-Sinai Medical Center and University of California at Los Angeles, Los Angeles, CA, USA.
- 3) Coomassie blue stained gel of total proteins produced in A549 (lanes 1-6) and HeLa (lanes 7-12) cells infected with Ad5.CMV5-R1 (lanes 2-6, 8-12). Cells were mock infected (lane 1 and 7) or infected at MOIs of 50 (lane 2, 8), 100 (lane 3, 9), 200 (lane 4, 10), 400 (lane 5, 11), and 800 (lane 6, 12). Recombinant R1 production is 30-35% TCP at the highest MOI tested. Courtesy of Bernard Massie, Biotechnology Research Institute, Montreal, Quebec, Canada.

# Target: Immuno- deficiency

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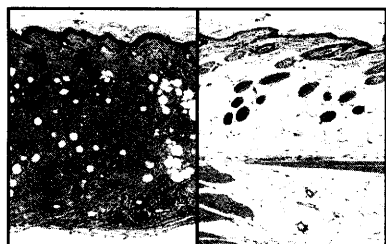
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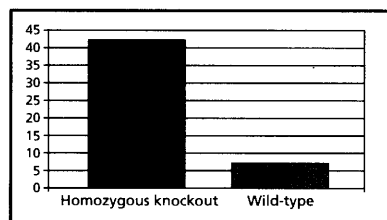
## Phenotypic analysis Gene: Phosphatase

Homozygous knockout Wild-type



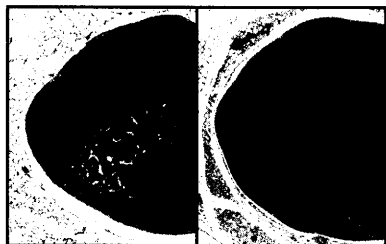
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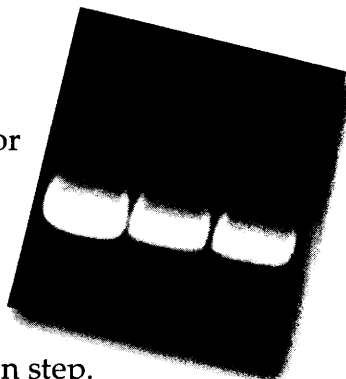
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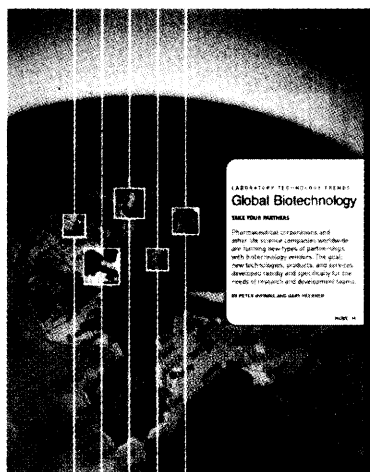
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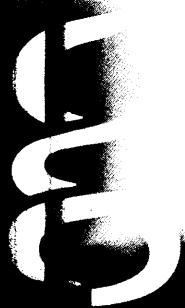
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## **FAMRI ANNOUNCES THE SECOND YEAR CLINICAL RESEARCH AWARDS**

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](mailto: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.

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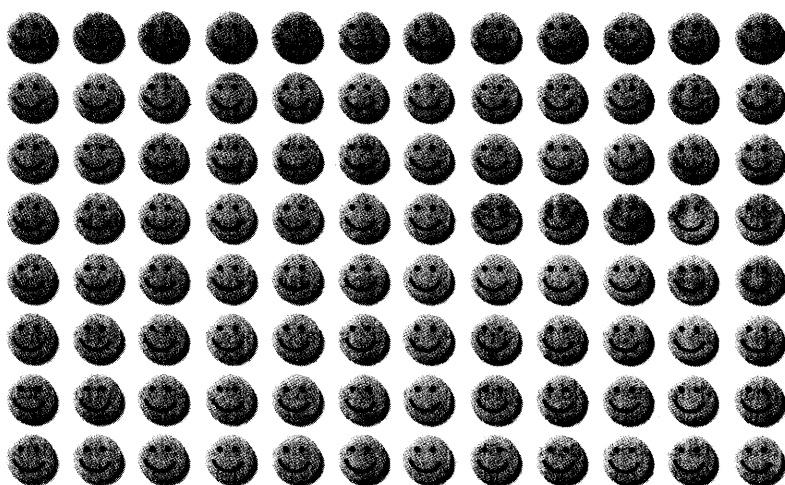
FAMRI established the CIA to stimulate novel medical and clinical scientific research studies on the effects of exposure to secondhand tobacco smoke. While considerable government and non-government funding is available to support established mainstream biomedical research projects, funds for high-risk 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 disciplinary 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.

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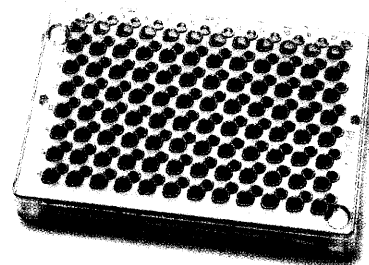
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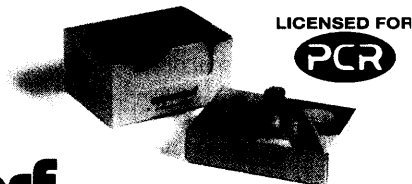
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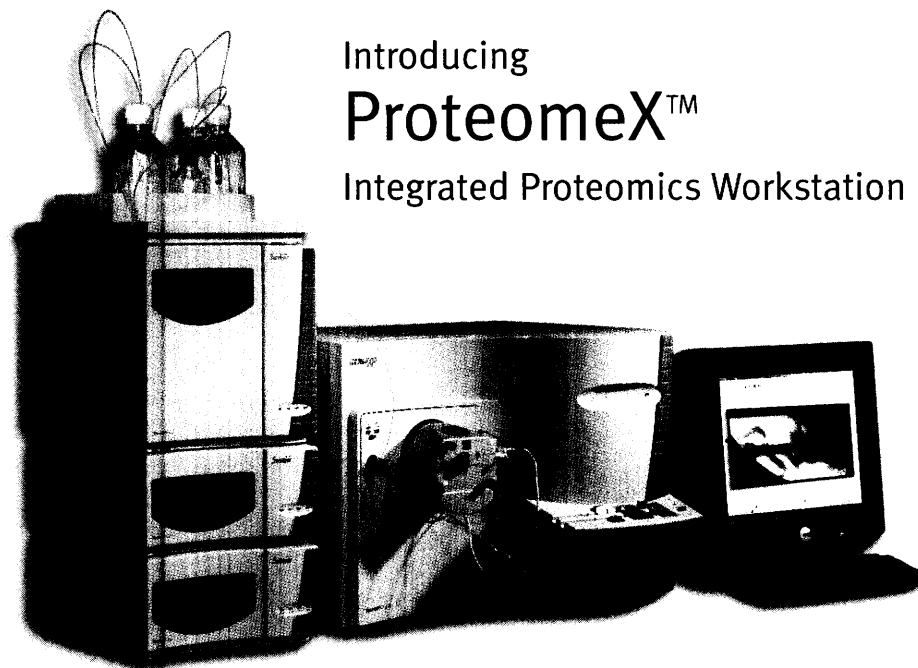
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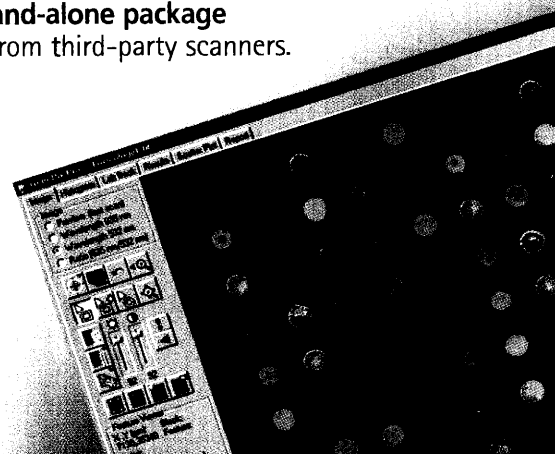
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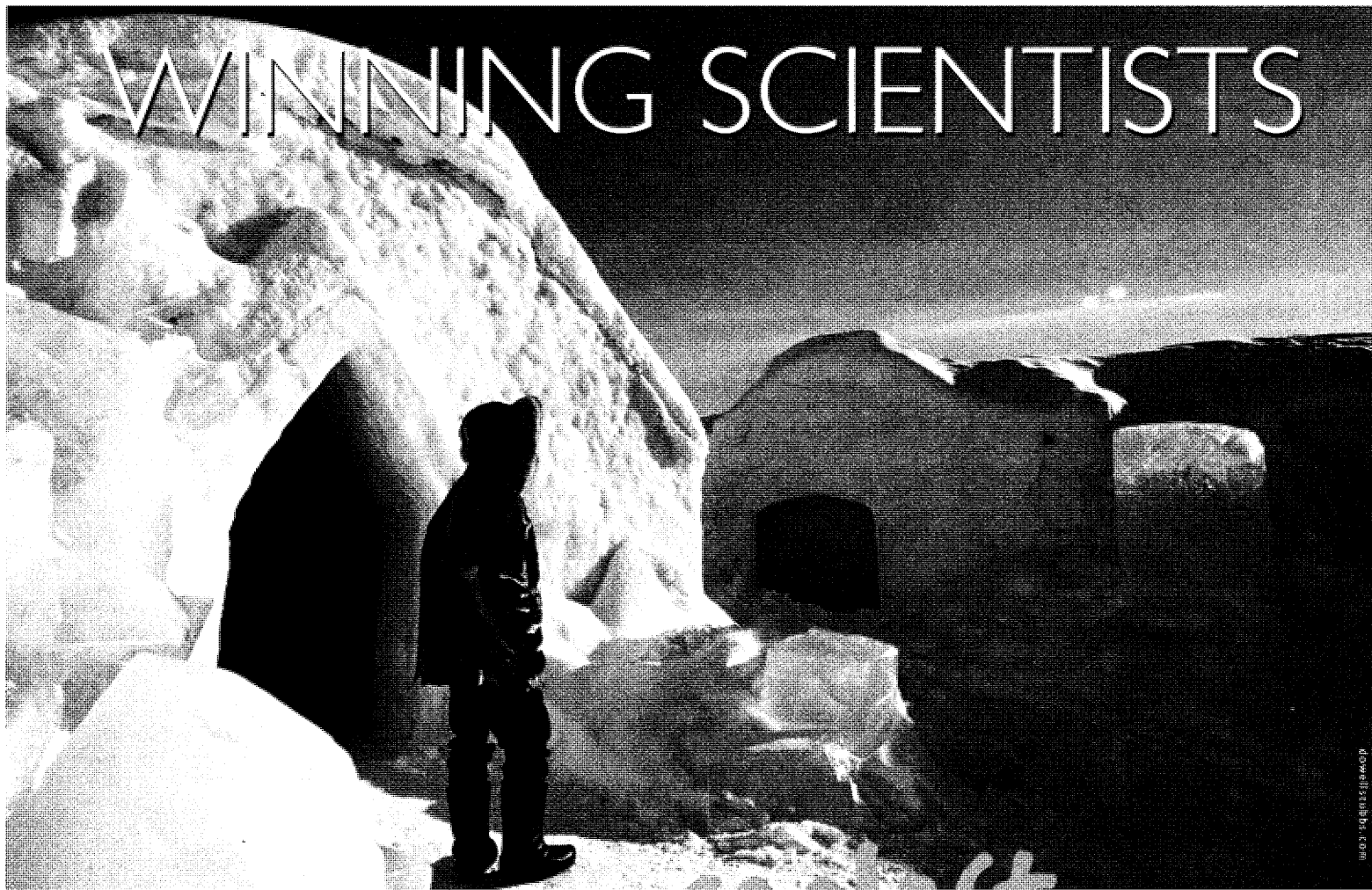
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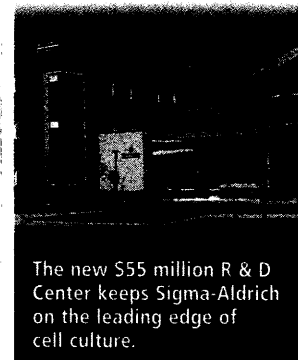
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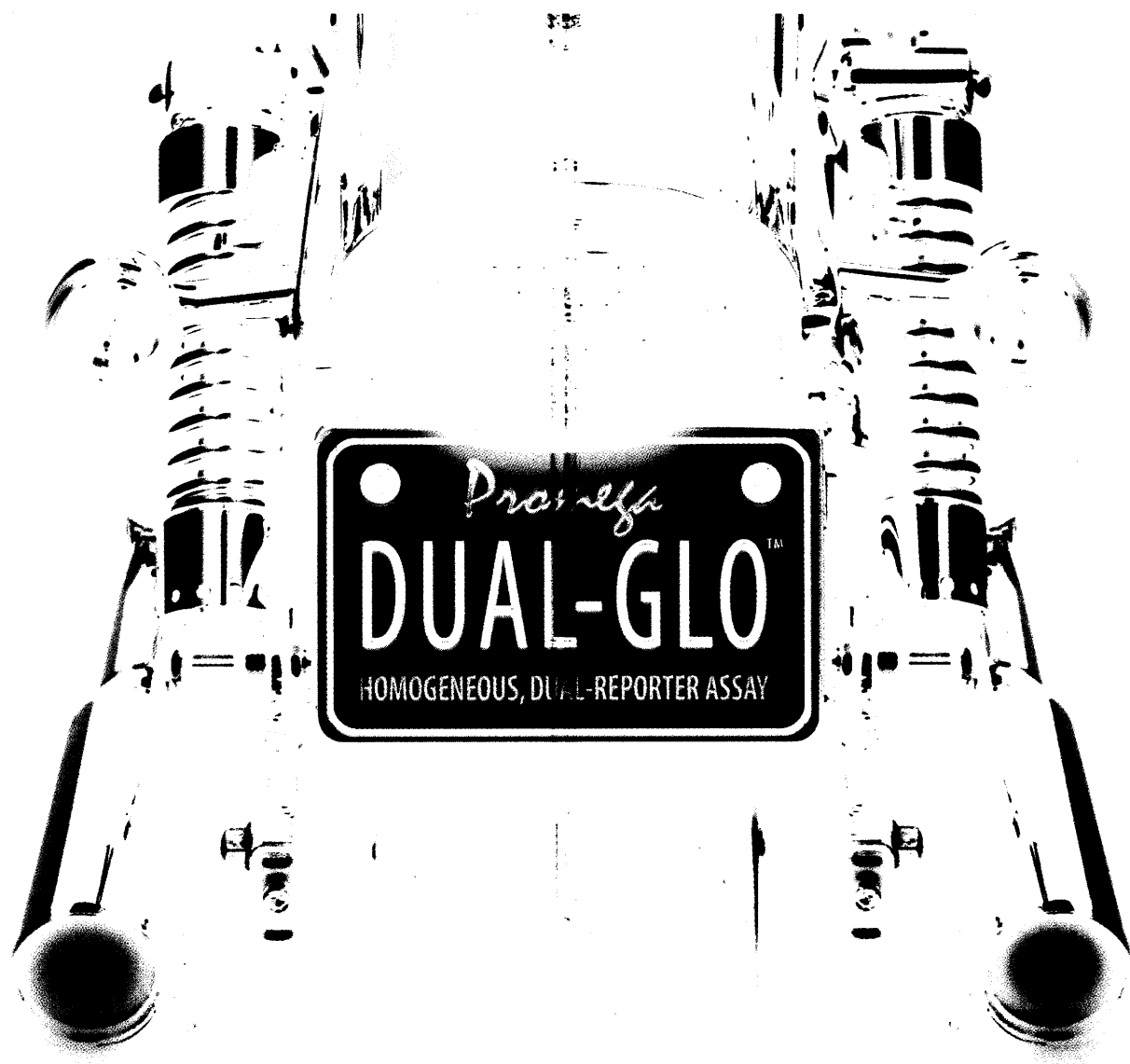
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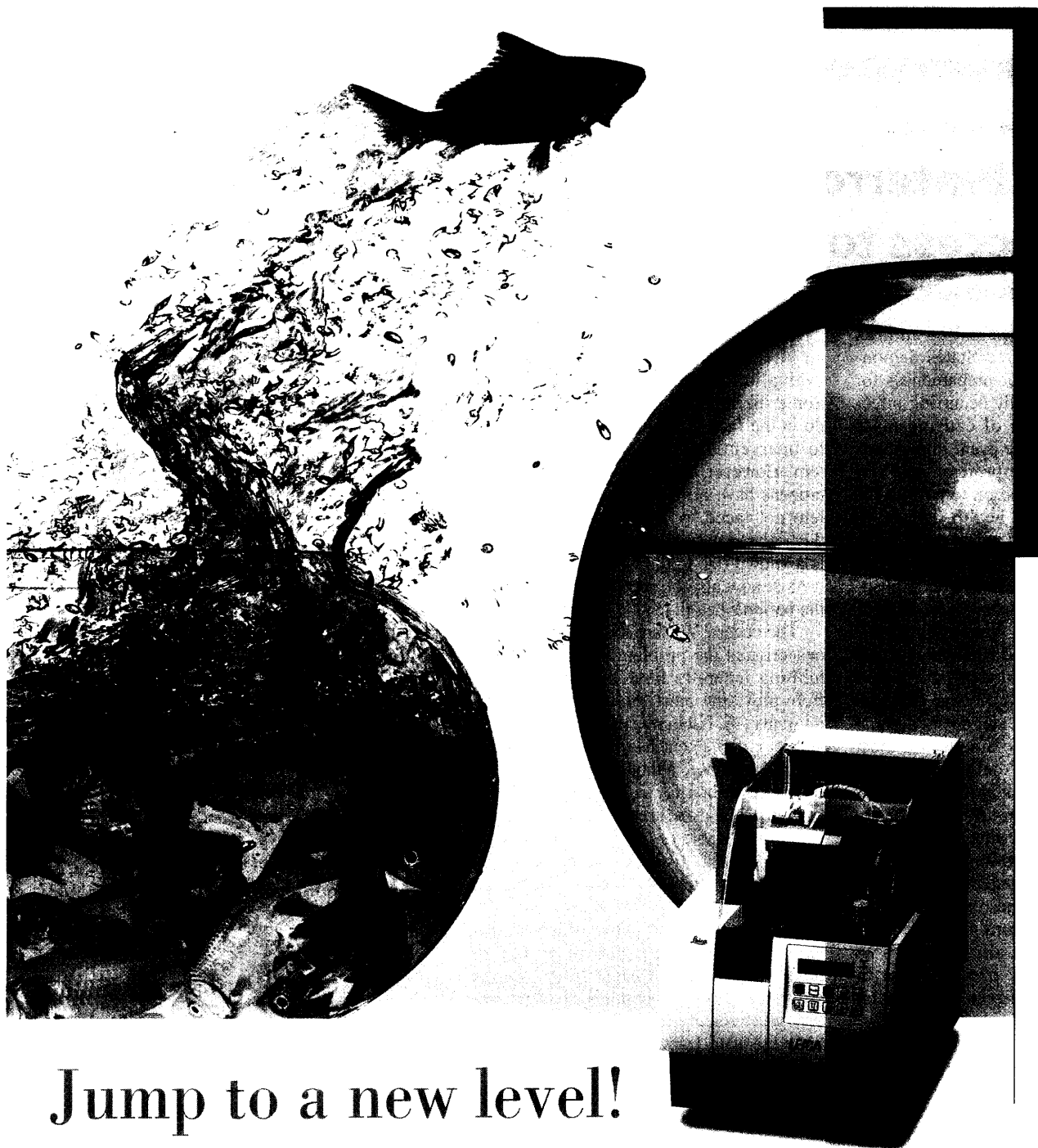
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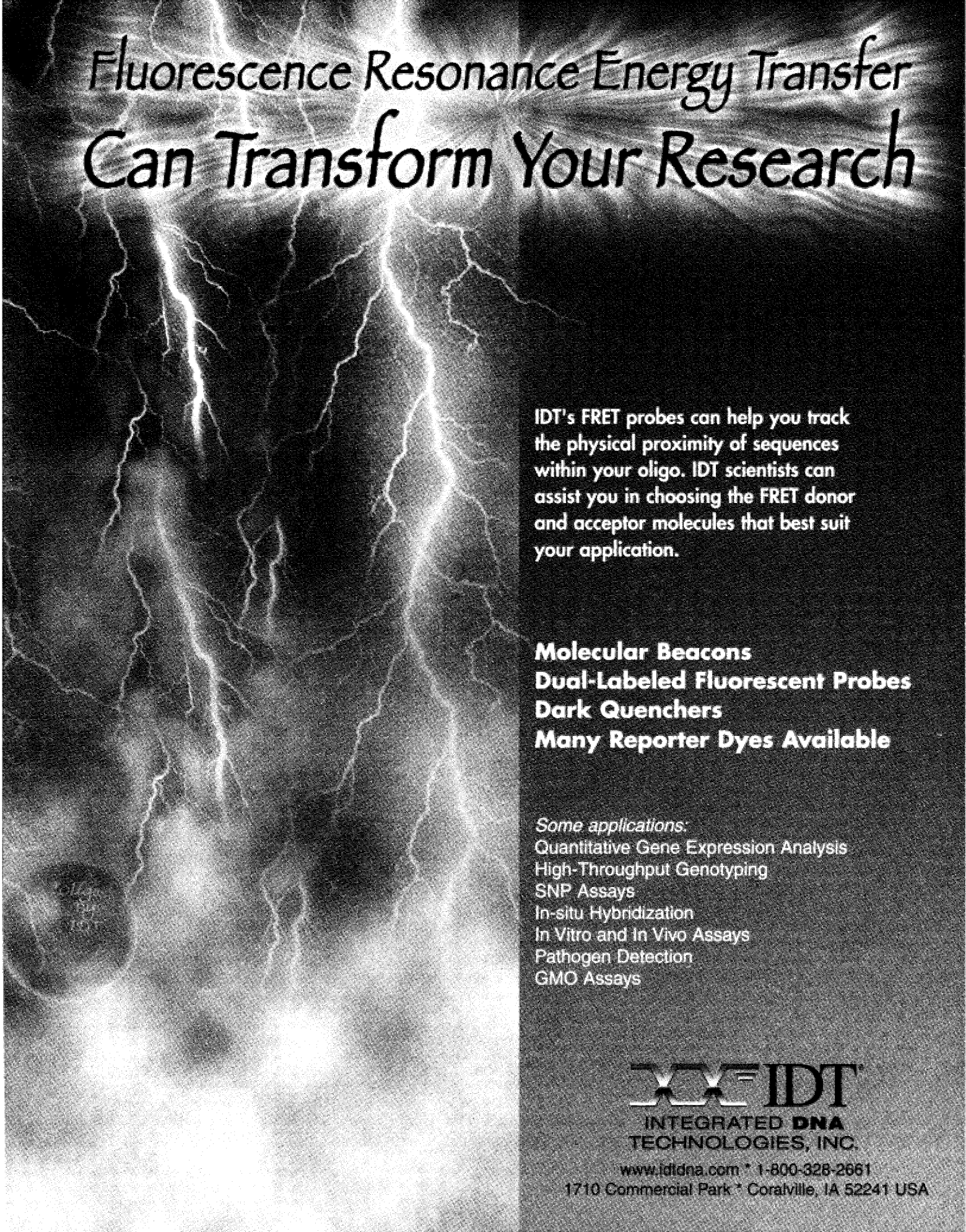
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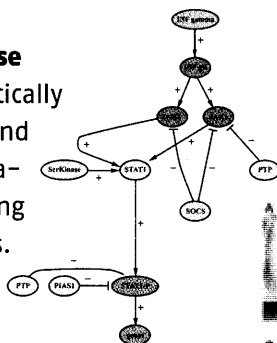
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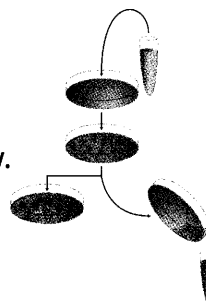
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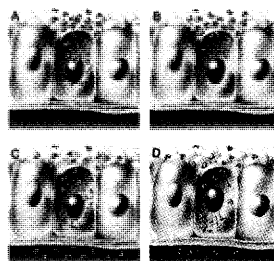


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### PROGRAM OF RESEARCH SUPPORT

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The Human Frontier Science Program (HFSP) supports basic research aimed at **elucidating the complex mechanisms of living organisms.** Emphasis is placed on novel, innovative and interdisciplinary approaches to basic research which involve scientific exchanges across national boundaries.

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#### **Deadline for Long-Term Fellowship Applications: 2 SEPTEMBER 2002**

*(awards to be announced in April 2003)*

#### CAREER DEVELOPMENT AWARDS

The Career Development Award (CDA) is designed to enable former HFSP fellows to establish themselves as independent young investigators in their home countries. HFSP Fellows awarded in 2000 who have or will have a position in their home country in which they will be able to pursue independent research are eligible to apply. The CDA provides \$180,000 USD for salary and research support over a 2-3 year period.

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Provide up to three months of support to learn new techniques or establish new collaborations in another country. Applications are accepted throughout the year.

#### RESEARCH GRANTS

In 2001, the HFSP established a new procedure for the grant program requiring a letter of intent in March of each year and submission of complete applications **by invitation only** in mid-September. The next call for letters of intent for Award Year 2004 will appear in December 2002. Two grant schemes are supported. **Young Investigators' Grants** are for teams of scientists who are all within 5 years of establishing an independent laboratory. Successful teams will receive \$250,000 per year for the entire team. **Program Grants** are awarded to independent scientists at all stages of their careers, and provide up to \$500,000 per year for the entire team.

\*Current supporting countries include Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Japan, Luxembourg, the Netherlands, Portugal, the Republic of Ireland, Spain, Sweden, Switzerland, the United Kingdom and the United States.

Guidelines and application forms are available on the HFSP web site ([www.hfsp.org](http://www.hfsp.org))



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—Brian R. Shmaefsky

The author is in the Department of Biology & Environmental Sciences, Kingwood College, Kingwood, TX 77339-3801, USA. E-mail: [brian.shmaefsky@nhmccd.edu](mailto:brian.shmaefsky@nhmccd.edu)

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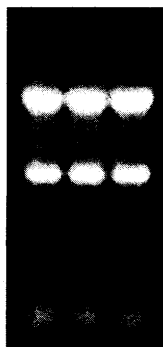
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