8 June 2001

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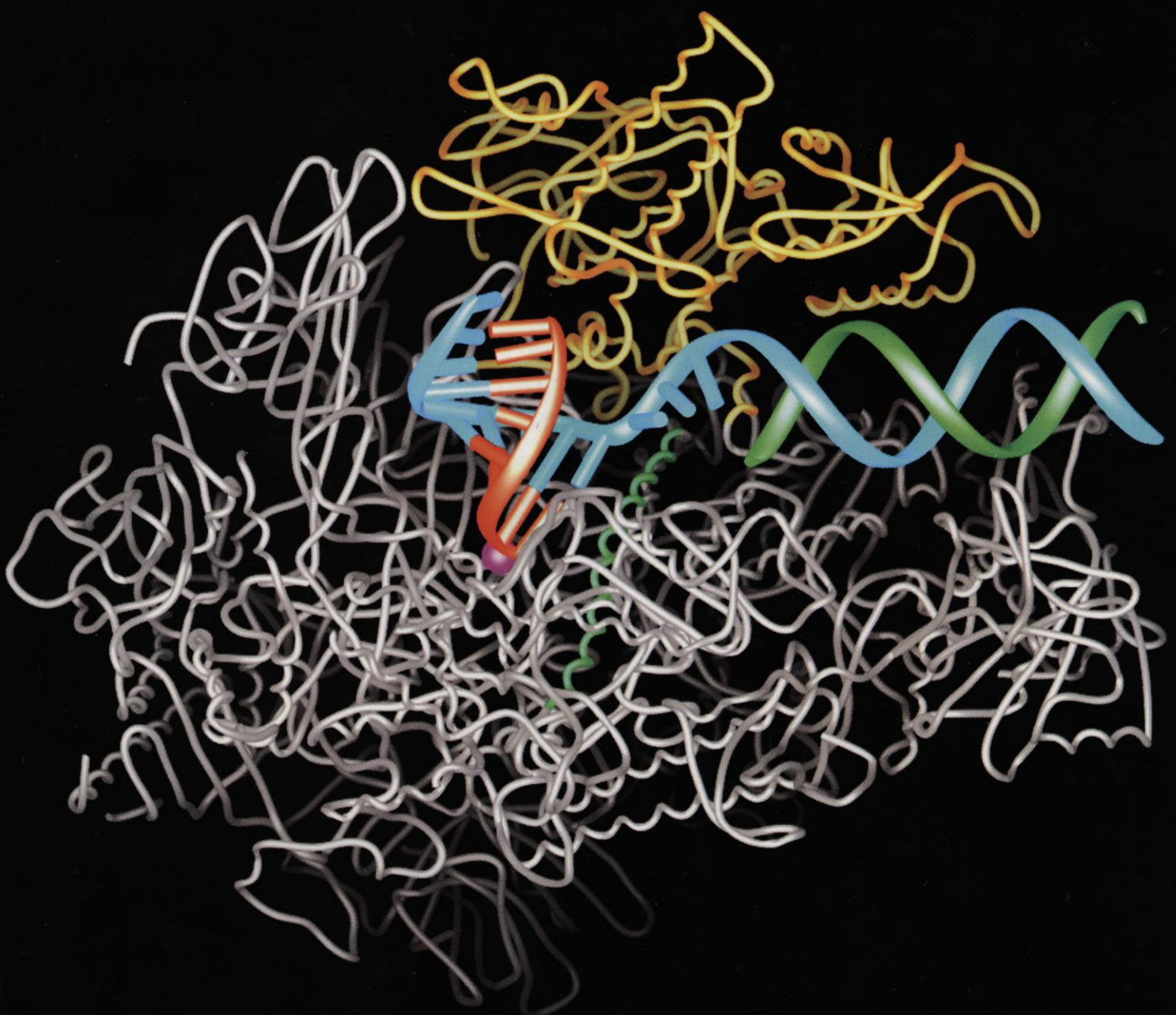
Pages 1785–1952 $9



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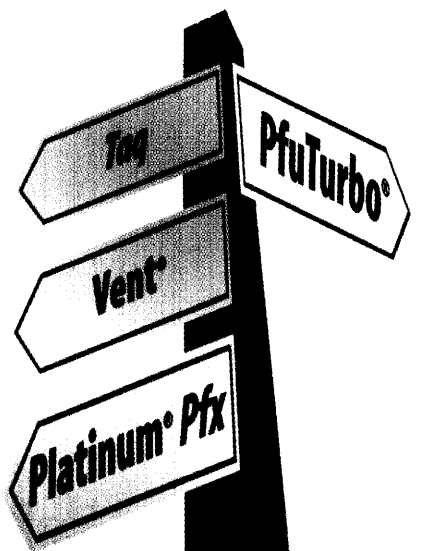

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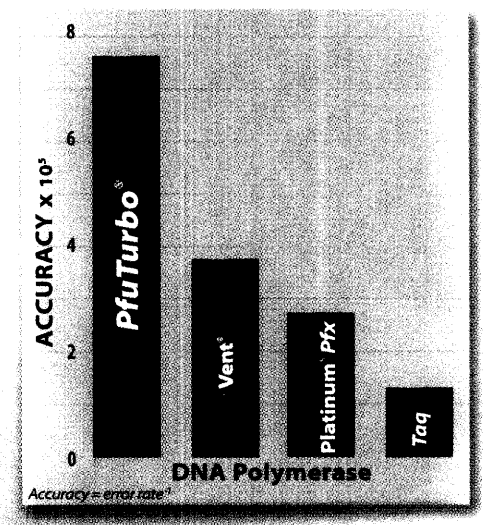

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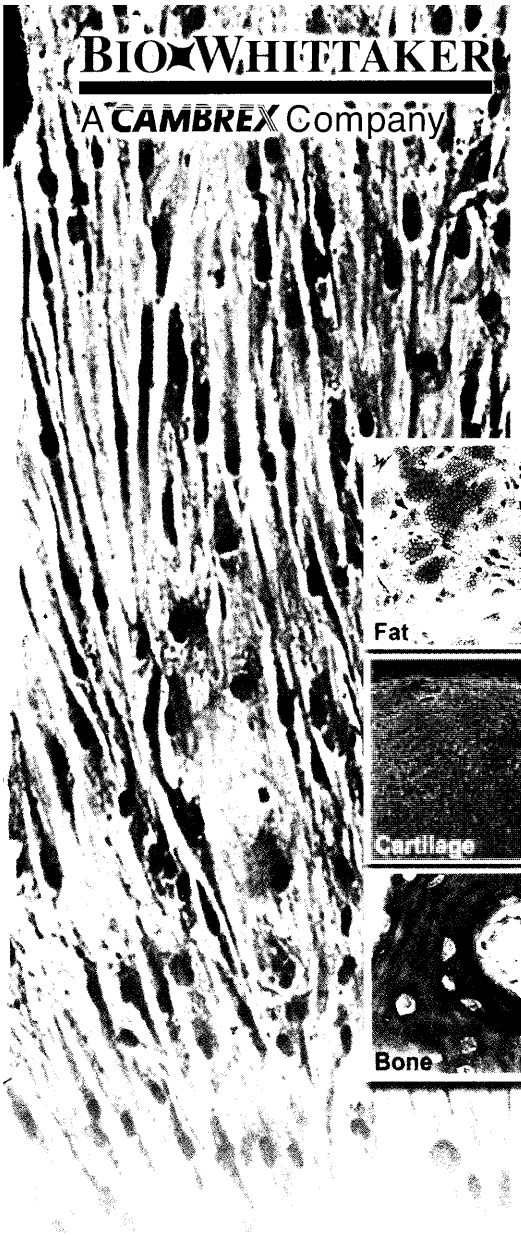

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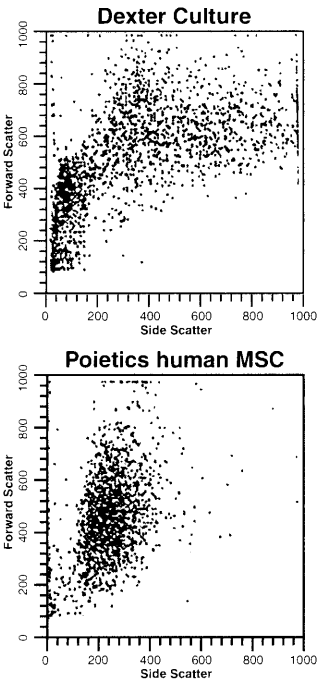

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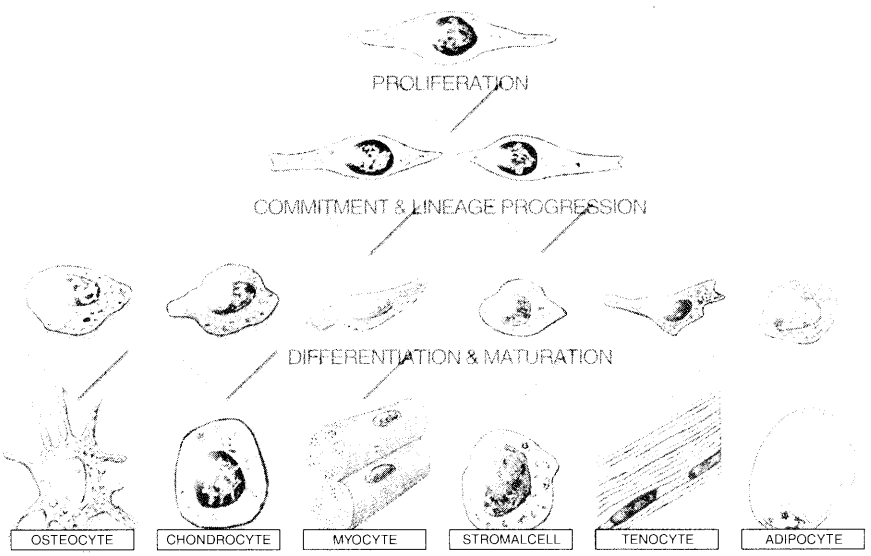

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Science

Volume 292 8 June 2001 Number 5523

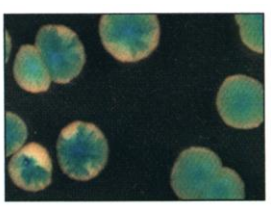
NEWS

1820
Ethical cure-all?

NEWS OF THE WEEK

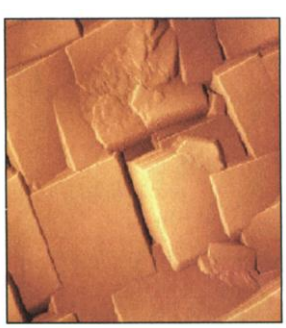
NEWS FOCUS

1824
On the fast track



SCIENCE'S COMPASS

1847
A bright future for diamond

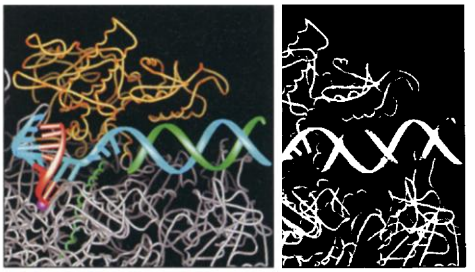


POLICY FORUM

BOOKS *ET AL.*

PERSPECTIVES

REVIEW



1910

Getting i
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RESEARCH

RESEARCH ARTICLE

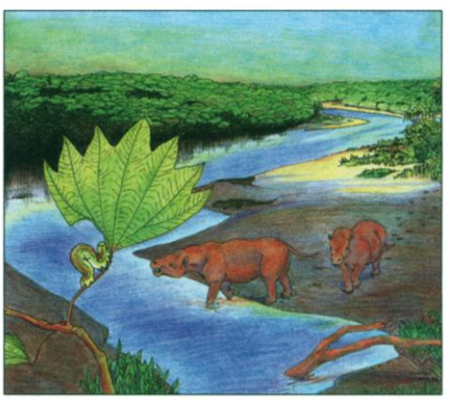
REPORTS

COVER 1876

The enzyme RNA polymerase II in the act of transcribing a gene. X-ray crystal structure comprises the protein (gray, except for orange "clamp" and green "bridge" helix), DNA (blue template strand, green nontemplate strand), and RNA (red). The pink sphere is an active center Mg^{2+} ion. Double-stranded DNA enters from the right and unwinds before the active center. The unwound nontemplate DNA strand is obscured by motion or disorder. [Adapted from Fig. 2C of Gnatt *et al.*]

1888

Megafauna overkill



Retrieving memories through the mushroom body

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Collapse of the California Current During Glacial Maxima Linked to Climate Change on Land T. D. Herbert *et al.*

PERSPECTIVE: **Ice Ages, the California Current, and Devils Hole—It's a Matter of Timing** D. W. Lea

California coastal ocean temperatures changed by up to 8°C over the past 500,000 years and seem to have warmed thousands of years before ice sheet melting during the past five deglaciations.

The Role of *Drosophila* Mushroom Body Signaling in Olfactory Memory S. E. McGuire, P. T. Le, R. L. Davis

The mushroom body, a structure within the fly's brain, is necessary for memory retrieval but not memory acquisition or consolidation.

Femtomolar Sensitivity of Metalloregulatory Proteins Controlling Zinc Homeostasis C. E. Outten and T. V. O'Halloran

Zinc sensors in bacteria respond to the metal at concentrations far below one molecule of free zinc per bacterial cell.

TECHNICAL COMMENTS

Multisensory Integration and Crossmodal Attention Effects in the Human Brain

Macaluso *et al.* (Reports, 18 Aug. 2000, p. 1206) showed that a tactile stimulus to the right hand, presented simultaneously with a visual stimulus in the right visual field, enhances activity in the visual cortex, a pattern they attributed to neuronal input from higher multimodal association cortex areas back-projecting onto the visual cortex. The result, they suggested, "provides a neural explanation for crossmodal links in spatial attention." McDonald *et al.* comment that such a conclusion may be premature because of the stimulus parameters chosen; in particular, they argue, because the experiments presented "relatively long-lasting visual and tactile stimuli" simultaneously, the observed neural interactions could reflect multisensory integration rather than spatial attention effects. Macaluso *et al.*, in a response, maintain that the issues raised by McDonald *et al.* are largely "terminological." They also argue that, contrary to the comment's suggestion, a "simple timing rule" for stimuli is not sufficient "for distinguishing between integration and exogenous attention effects."

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/1791a

science's stke www.stke.org

Review: *S*-Nitrosylation Is Emerging as a Specific and Fundamental Posttranslational Protein Modification P. Lane, G. Hao, S. S. Gross

S-nitrosylation, a regulator of cell activity to rival *O*-phosphorylation.

Protocol: The Biotin Switch Method for the Detection of *S*-Nitrosylated Proteins S. R. Jaffrey and S. H. Snyder

A new method to detect the labile posttranslational modification *S*-nitrosylation.

science's next wave www.nextwave.org

UK: Are British Scientists Language Dunces? H. Marshall

Unless UK science students do something to combat their traditional lack of linguistic ability, they could be missing out in an increasingly European job market.

Canada: Getting Started in a Start-Up R. Wintle

Although junior scientists interested in industry careers enjoy many opportunities, finding that first start-up position is not always easy.

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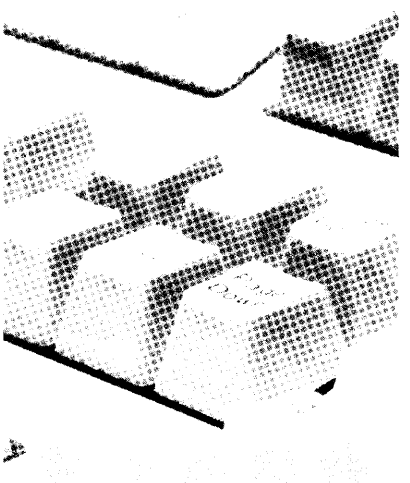

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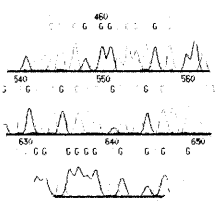

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THIS WEEK IN Science

edited by Phil Szuromi

Not-So-Clear Skies

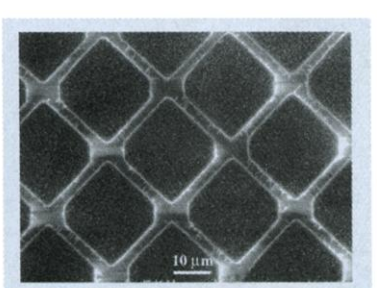
The hydroxyl radical OH, the principal chemical oxidant in the atmosphere, reacts with organic hydrocarbons, carbon monoxide, methane, and most other trace constituents with appreciable lifetimes. Although OH can be measured directly at the local scale, estimates of its hemispheric or worldwide distribution must be made by measuring the concentration of an atmospheric species with which it reacts at a known rate. Measurements by Prinn *et al.* (p. 1882) of one such species, methyl chloroform, show that the concentration of OH has been higher in the Southern Hemisphere than in the Northern Hemisphere for the past 20 years. Global OH concentrations rose during most of the 1980s but have declined to below 1978 concentrations during the past 10 years. This trend, whose origins are still poorly understood, implies that the ability of the atmosphere to cleanse itself of anthropogenic greenhouse gases is decreasing.

1863 1876 Making Messenger RNA

RNA polymerase II is the molecular machine responsible for all messenger RNA (mRNA) synthesis in eukaryotes. Cramer *et al.* (p. 1863) describe the structure of this large enzyme at 2.8 angstrom resolution, which allows the identification of most amino acid side chains, and Gnatt *et al.* (p. 1876) describe the structure of a complex caught in the act of transcription at 3.3 angstrom resolution (see the cover and the Perspective by Klug). The complex shows the position of the DNA duplex and the RNA-DNA hybrid. The polymerase is divided into four mobile modules that allow a clamp to be open in the uncomplexed structure, so that promoter DNA can enter, but that can close over the RNA and DNA in the complex. Together, the structures reveal protein features crucial in transcription and provide insight into how transcription is initiated, how the mRNA transcript is elongated, and how transcription factors are likely to interact with the polymerase.

Nanowire Lasers

Wide–band gap metal oxides prepared as low-dimensional structures could be used to create novel opto-electronic devices. Huang *et al.* (p. 1897) demonstrate room-temperature ultraviolet lasing from self-organized, oriented zinc oxide nanowire arrays deposited on sapphire substrates and synthesized using a simple vapor transport and condensation process. Grown in a preferred direction, these wide–band gap semiconductor nanowires form natural laser cavities with diameters varying from 20 to 150 nanometers and lengths up to 10 micrometers. Under optical excitation, surface-emitting lasing action is observed at a near-ultraviolet wavelength of ~385 nanometers with emission linewidth of less than 0.3 nanometer. This performance was achieved at a fairly low threshold of 40 kilowatts per square centimeter.



CREDIT: HUANG *ET AL.*

Making Diamond Shine

In addition to the desirable structural and thermal properties of diamond, its wide band gap makes it an attractive material for opto-electronic applications in the ultraviolet regime. Natural diamond is a p-type conductor (the charge carriers are "holes"), but the creation of its counterpart, n-type diamond (in which the carriers are electrons), has been particularly difficult because of problems in artificially doping diamond. This limitation has so far hindered the development of diamond-based opto-electronics. Koizumi *et al.* (p. 1899; see the Perspective by John) report on the preparation of n-type diamond grown epitaxially on a p-type diamond substrate that exhibits the electrical characteristics of a good pn junction. They show that the junction emits ultraviolet light when placed under forward bias.

Overkill of Pleistocene Megafauna

The majority of species of large land mammals, reptiles, and birds (mostly greater than 45 kilograms in weight and referred to as the megafauna) on the major continents, such as Australia and North America, went extinct over a time period of thousands of years. This extinction has usually been attributed to the arrival, expansion, and migration of human populations who hunted the megafauna, but it has been difficult to eliminate other possible causes for megafaunal extinction, such as climate change. Two reports provide evidence for anthropogenic overkill as a primary cause in North America and Australia (see the news story by Dayton and the book review by Pimm). Roberts *et al.* (p. 1888) dated megafaunal burial sites across the Australian continent and estimated extinction around 46,400 years ago; 10,000 years after the arrival of humans, but about 23,000 years before the Last Glacial Maximum. The rapid extinction of some 30 large mammalian herbivore species in North America at the end of the Pleistocene 12,000 to 13,000 years ago has been attributed both to climate change and to hunting by humans. Using a computer simulation model, Alroy (p. 1893) shows that given simple assumptions about human and prey species distributions and ecology, the inference of a major mass extinction caused by hunting might be hard to avoid. The simulation model, which unites population dynamics, ecology, conservation, and anthropology, shows that humans even at low densities are capable of precipitating the collapse of prey populations.

Rarely Sharing Their Genes?

The possibility of transfer of genes across species (lateral gene transfer) is of interest in understanding the evolution of species and in considering the possibility that bacterial infections can result in the transfer of genetic material to humans or other hosts. Salzberg *et al.* (p. 1903; see the Perspective by Andersson *et al.*), in a careful analysis of all available sequences of the human genome, present evidence that

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CONTINUED ON PAGE 1795

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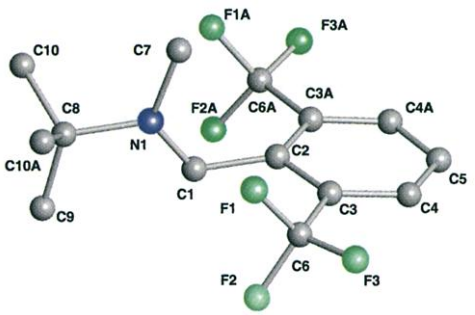
fewer than 50 genes are shared exclusively by bacteria and humans and are candidates for being the product of lateral transfer. This finding reduces previous estimates, but alternative explanations—sampling effects, gene loss, and rate variation within a genome—still exist.

Watching While the Other Works

Carbenes, in which a carbon atom forms only two single bonds and thus carries two nonbonding electrons, are highly reactive species that were long thought to exist only transiently, as is the case for the simplest carbene, CH_2. However, carbenes can now be isolated, either as the spin-paired singlet and unpaired triplet forms, by carefully choosing the two substituent groups on the carbon atom to balance and shift electron density. Solé *et al.* (p. 1901; see the Perspective by Wentrup) now show that singlet carbenes can be stabilized by tuning only one of the substituents, which is designed to have both π-bond donor and σ-bond acceptor character; the other substituent is a mere spectator. This finding should greatly expand the number of stable carbenes that can be prepared and expand their synthetic utility.



Helper T Cells Decide Their Own Fate

Helper CD4 T cells (T_H cells) acquire distinct phenotypes, depending on the prevailing cytokine environment, and two models exist to explain how this might occur. The first is an "instructive" model, which proposes that cytokines direct cell fate by launching a program of differentiation and gene transcription. The second is a "selective" model which suggests that T cells undergo an essentially stochastic fate determination that is then supported by the appropriate set of cytokines. Mullen *et al.* (p. 1907) present evidence for a selective model of T_H1 development. They demonstrate that expression of the hallmark T_H1 cytokine interferon-γ (IFN-γ) and a recently identified master regulator gene, T-bet, are independent of interleukin-12 (IL-12) and the associated protein STAT-4 (signal transducer and activator of transcription 4). Retroviral expression of T-bet directly initiated IL-12–autonomous induction of IFN-γ expression, which could then be secured with the provision of a IL-12/Stat-4 signal. The stabilization of IFN-γ expression by IL-12/Stat-4 correlated with the activity of CBP (CREB-binding protein), a cofactor with intrinsic actyltransferase and chromatin-remodeling activity. These findings suggest that cytokines may be critical in nurturing committed T_H cells, rather than dictating to those that have not yet made a decision.

Extra p53 Export Route

The tumor suppressor p53 is one of the best-characterized proteins, but it can still come up with a few surprises. Zhang and Xiong (p. 1910; see the Perspective by Gottifredi and Prives) identified a second nuclear export signal (NES) in p53. This NES, which is close to the amino-terminus of the protein, is inactivated in response to phosphorylation, which is itself stimulated by DNA damage. The work elucidates one of the mechanisms by which cellular injury controls the distribution of this key protein in the body's cellular defenses against malignancy.

Clicking on a Mouse Model

In recent years, certain human diseases have been linked to changes in particular chromosomal regions. However, many diseases involve multiple genetic loci, thus compounding the complexity of the problem. The mouse has proven to be a useful model for studying human disease. Using genotype and phenotype information from common inbred mouse strains, Grupe *et al.* (p. 1915; see the news story by Davenport) have developed a Web-accessible database that can be computationally analyzed to identify chromosomal regions regulating complex disease-related traits in mice. This molecular genetic analysis can be performed in milliseconds and does not require laborious, time-consuming, and costly genetic mouse studies.

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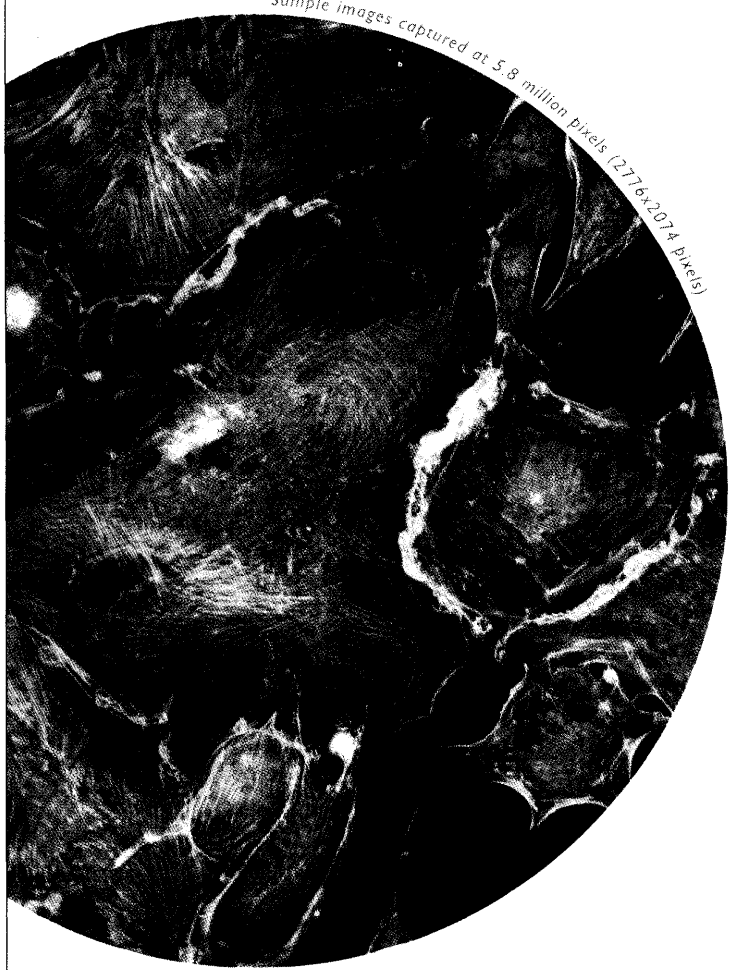

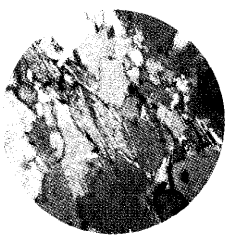

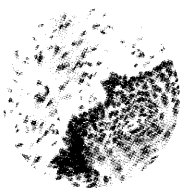

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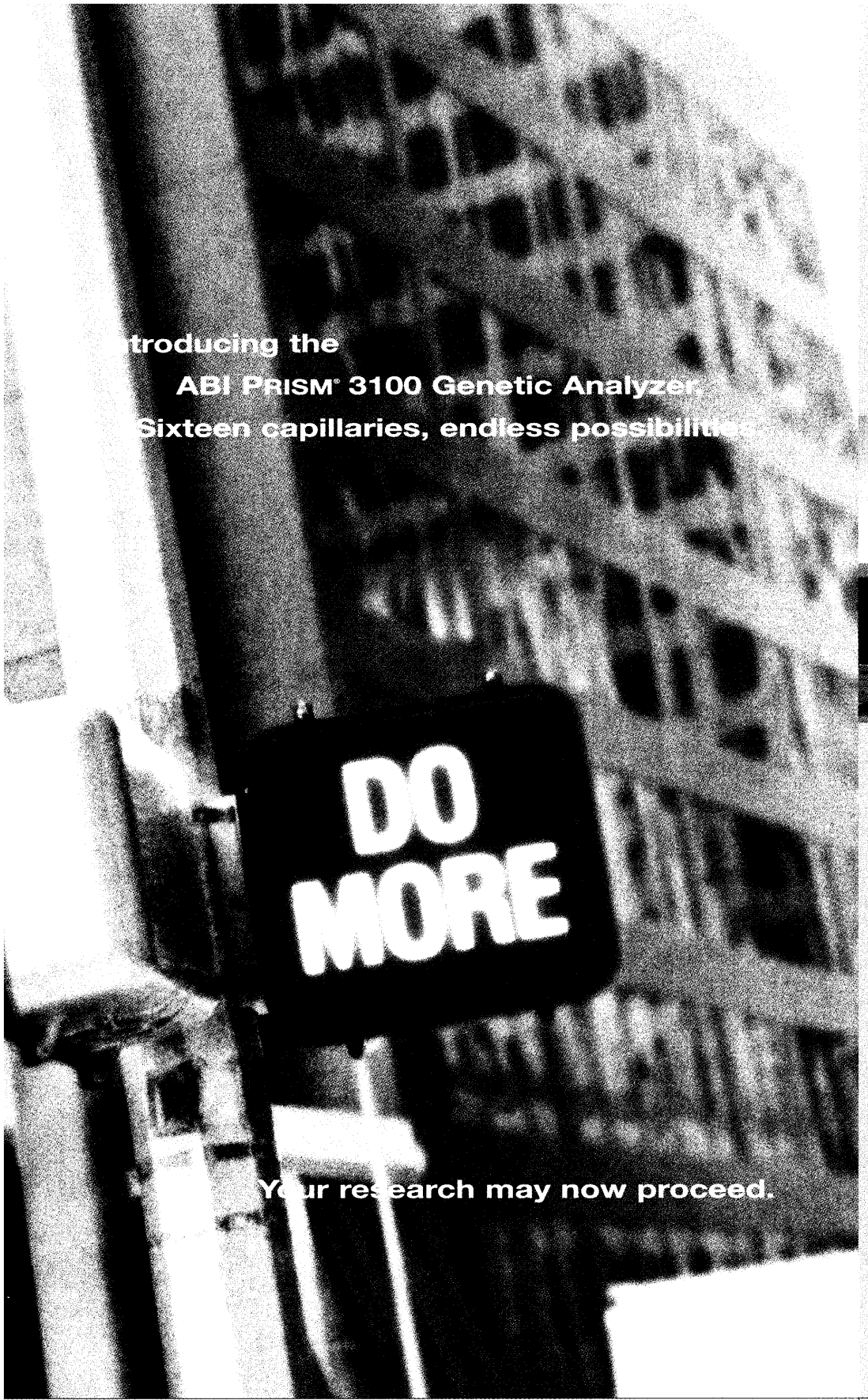

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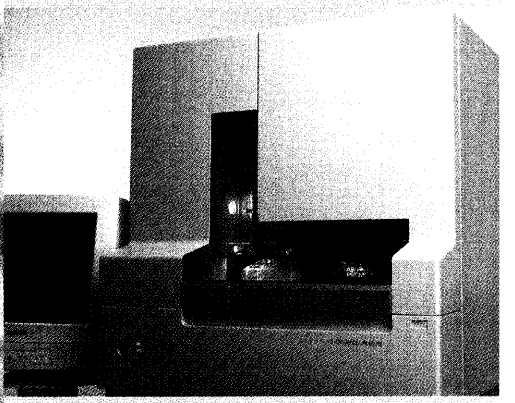

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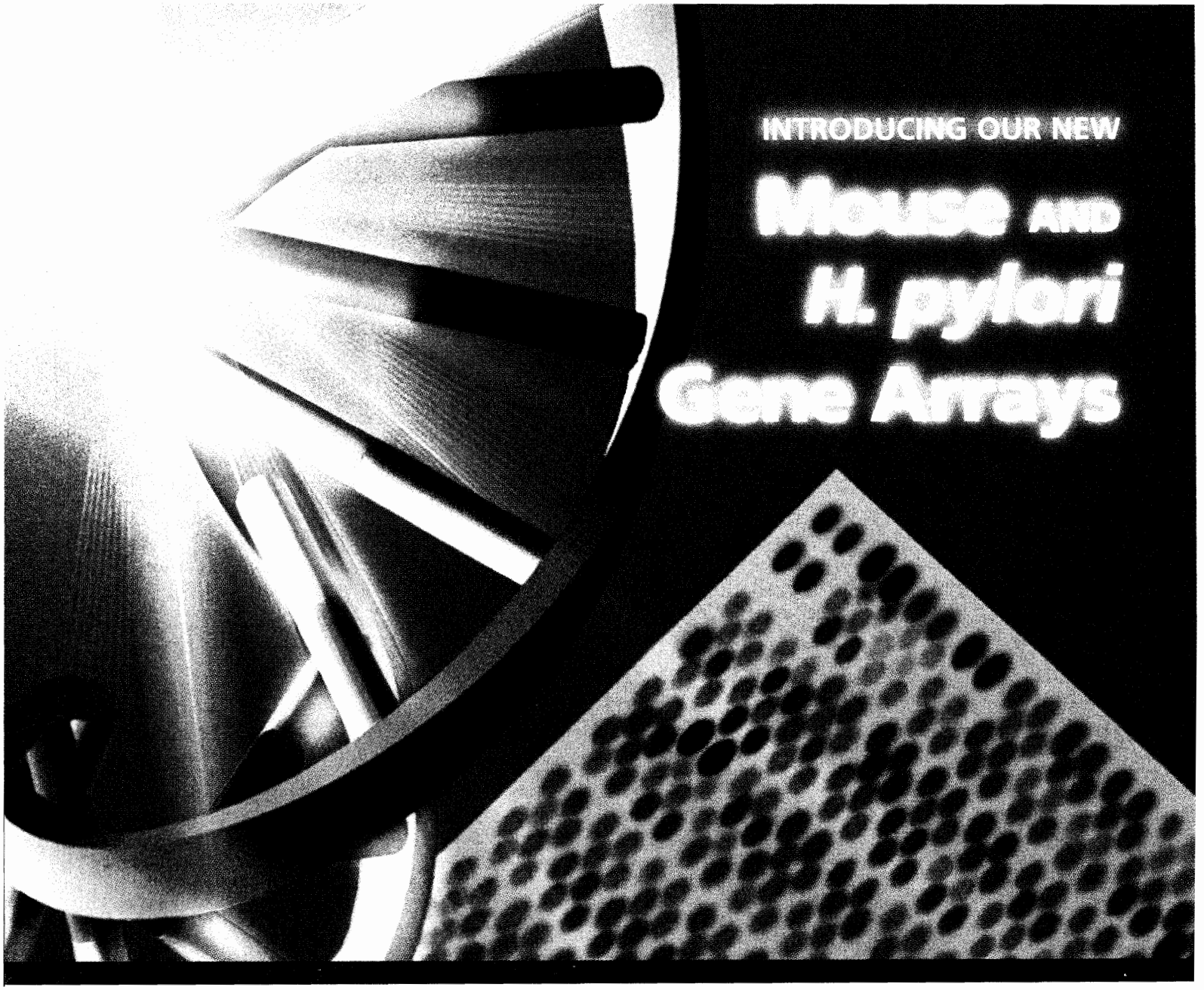

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Call for Proposals

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The National Foundation for Excellence in Scientific Research

SFI Fellows

Science Foundation Ireland (SFI) invites applications in Biotechnology and Information and Communication Technology (ICT) for SFI Fellow Awards from outstanding researchers in the research community in Ireland and around the world, including those in industry. The focus of the call is to identify a number of outstanding researchers in the relatively early stages of their careers who, together with their teams, will carry out their work in Public Research Bodies (including Universities and Inststutes of Technology) in Ireland.

Successful candidates for the awards will hold a research degree and will have significant research experience at postdoctoral level, or equivalent, for a period typically in the region of 4 to 8 years. He/she will be recognized as a researcher of great promise and be expected to have a number of major research achievements. He/she should be internationally recognized as having the potential, in time, to be the leader in his/her field. The assessment will be by international peer review.

The Foundation will fund all relevant costs for the SFI Fellow and a small team including salaries, equipment, consumables, collaboration and travel with an annual budget up to €325,000 (US$300,000), subject to a maximum of €1,625,000 (US$1,500,000) over 5 years (60 months). The typical team will include the SFI Fellow, postdoctoral/postgraduate researchers and technical support. The funding will be provided for a period of 3-5 years, subject to satisfactory performance as monitored by international experts and SFI.

The areas eligible for funding in this Call are:

Biotechnology

The Foundation is particularly interested in basic research which is fundamental to the advancement of Biotechnology in:

Signal Transduction in Cellular Contexts;

The Immune Process, including Molecular Medicine;

Functional Genomics

and the relevant underlying platform technologies (such as DNA chip array technology, proteomics, bioinformatics and structural biology). The Foundation is also prepared to consider outstanding proposals in other areas of fundamental importance to the advancement of Biotechnology.

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The Foundation is particularly interested in basic research which is fundamental to the advancement of ICT in:

Software Reliability in Complex Software-Intensive Systems;

Optical Transmission and Switching Technologies (including related Nanoscience).

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Applications

Applications are invited from high achieving researchers with outstanding potential as outlined above. This Call for Proposals is a 'rolling call' with no set closing date; applications may be submitted at any time and will be reviewed periodically.

Please refer to **www.sfi.ie** for more complete details of this Call for Proposals.

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Proposals, which can only be accepted on the Application Form provided, should be submitted to the Foundation at the following address:

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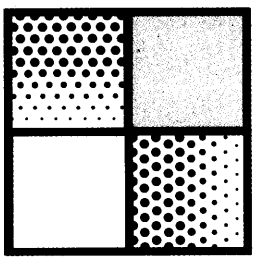

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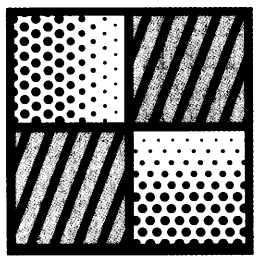

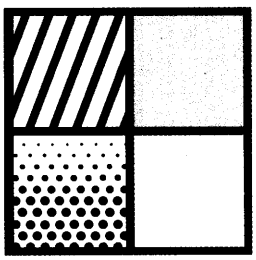

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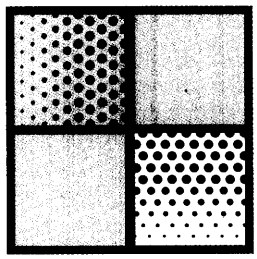
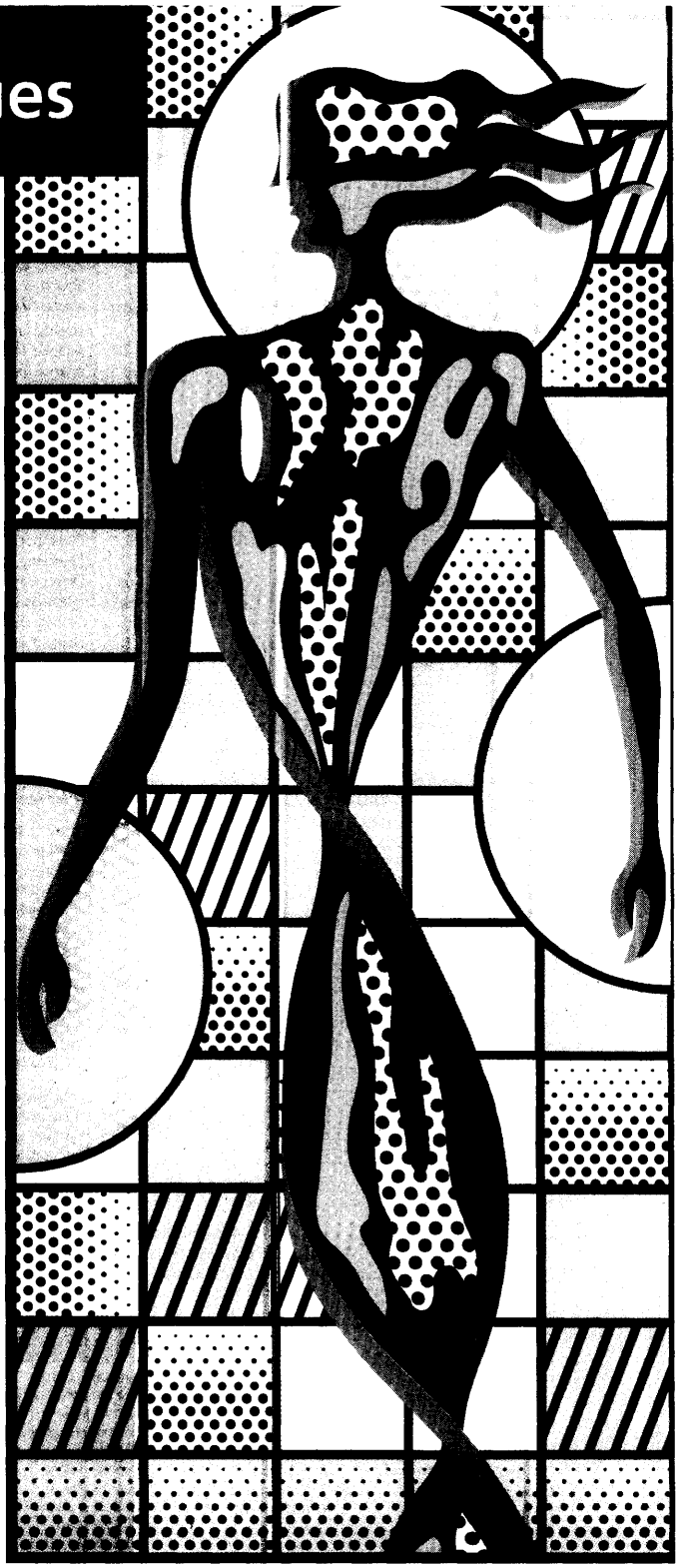


in normal and cancer tissues



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- **Analyze differential gene expression in tumor and normal tissues of the same patient**
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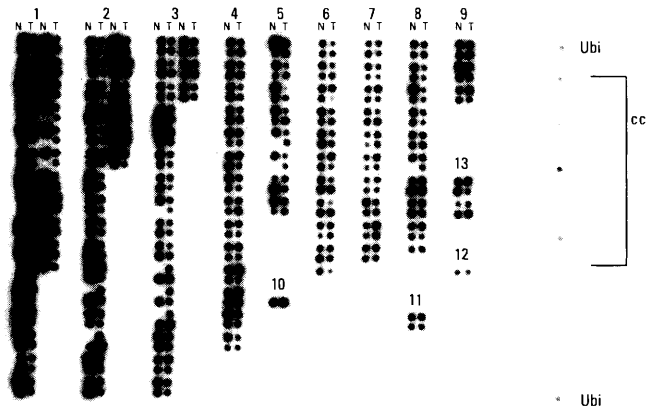

Figure 1. The Cancer Profiling Array demonstrates tissue-specific expression of gelsolin. The Cancer Profiling Array was hybridized with a radiolabeled probe for gelsolin. Hybridization signals were detected by phosphorimaging. Signifigant up regulation is clearly present in tumor samples from breast, uterine, and ovarian tissues. Numbers in columns indicate tissue types. 1: breast. 2: uterus. 3: colon. 4: stomach. 5: ovary. 6: lung. 7: kidney. 8: rectum. 9: thyroid gland. 10: cervix. 11: small intestine. 12: pancreas. 13: prostate. N = normal. T = tumor. Ubi = ubiquitin cDNA. cc = cancer cell line cDNAs.

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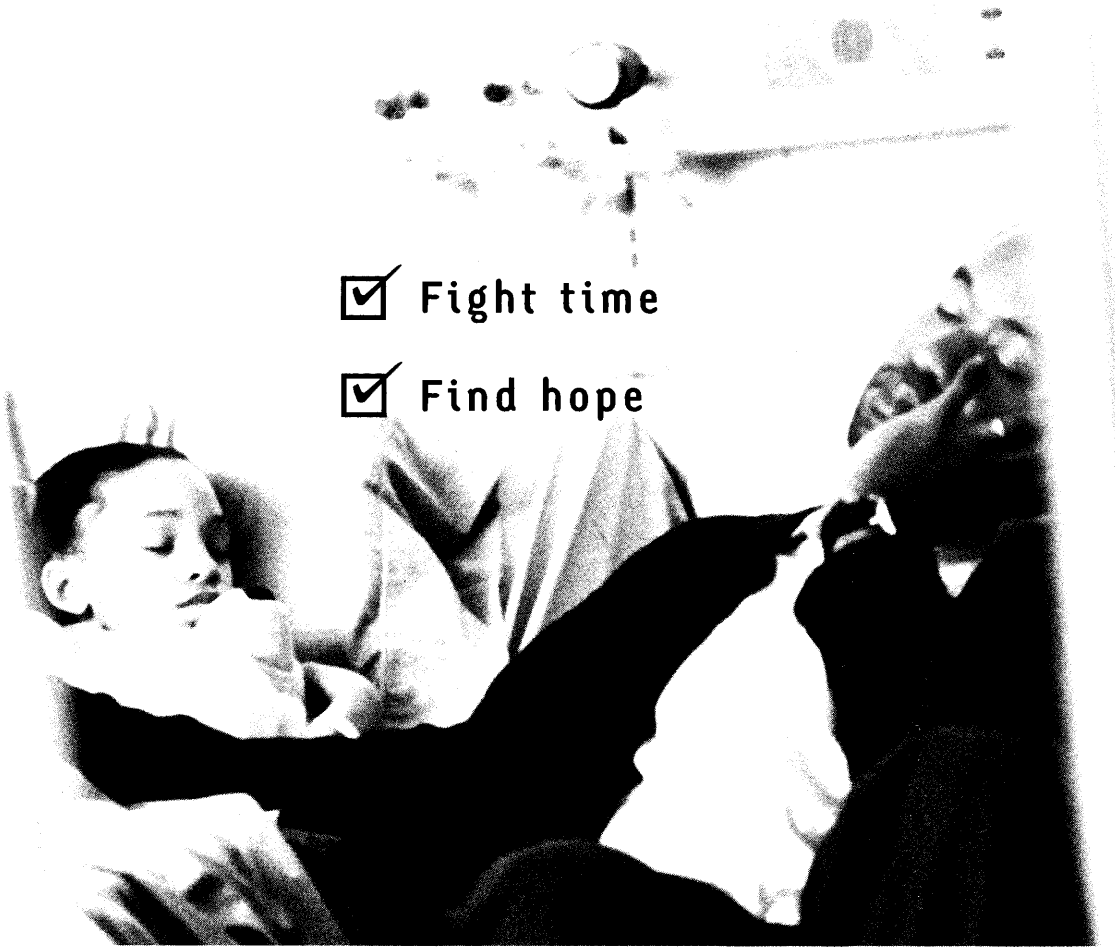

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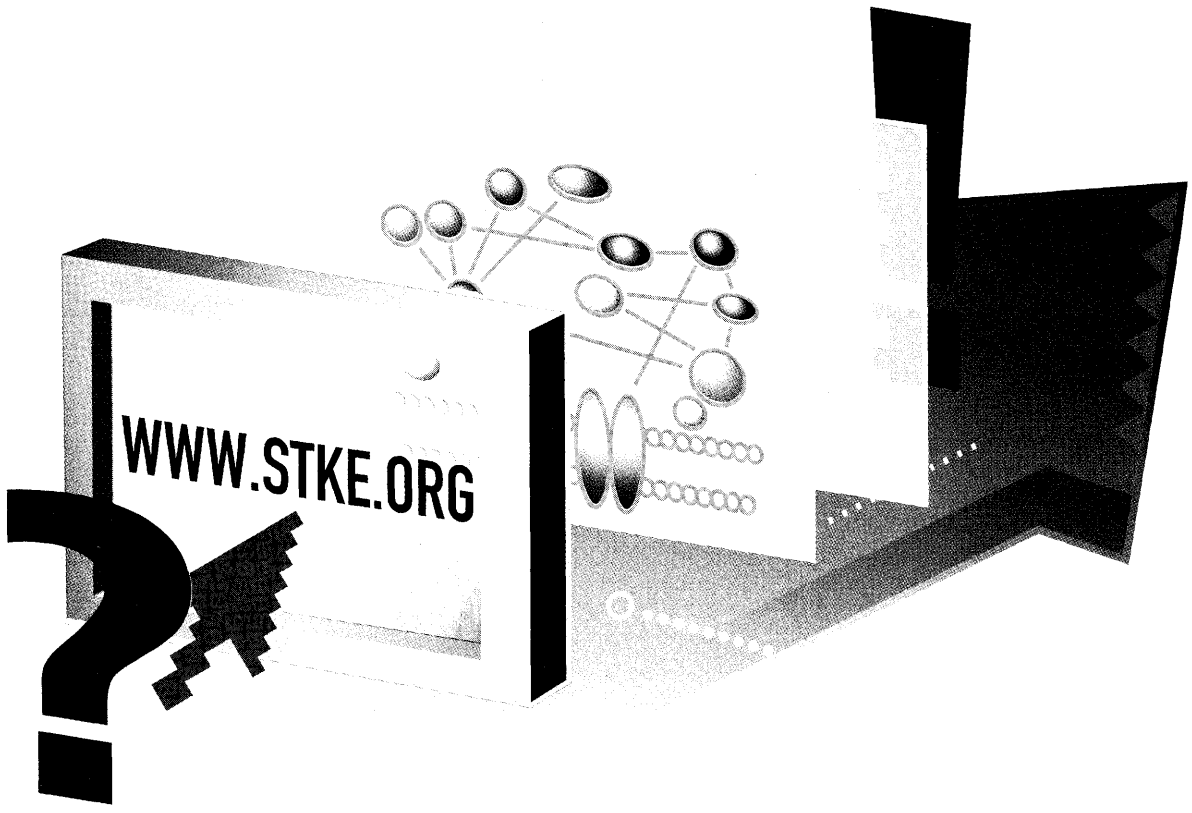

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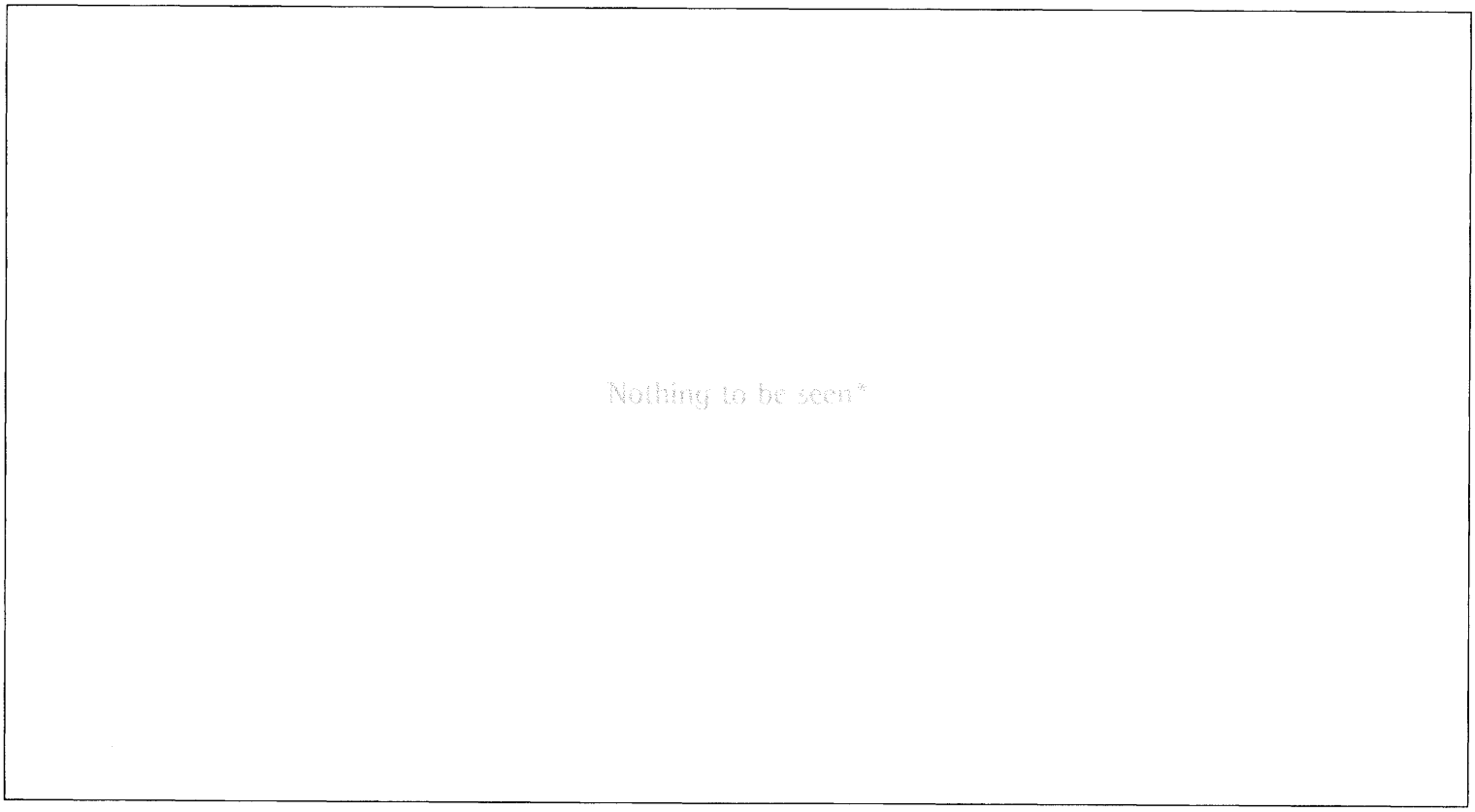

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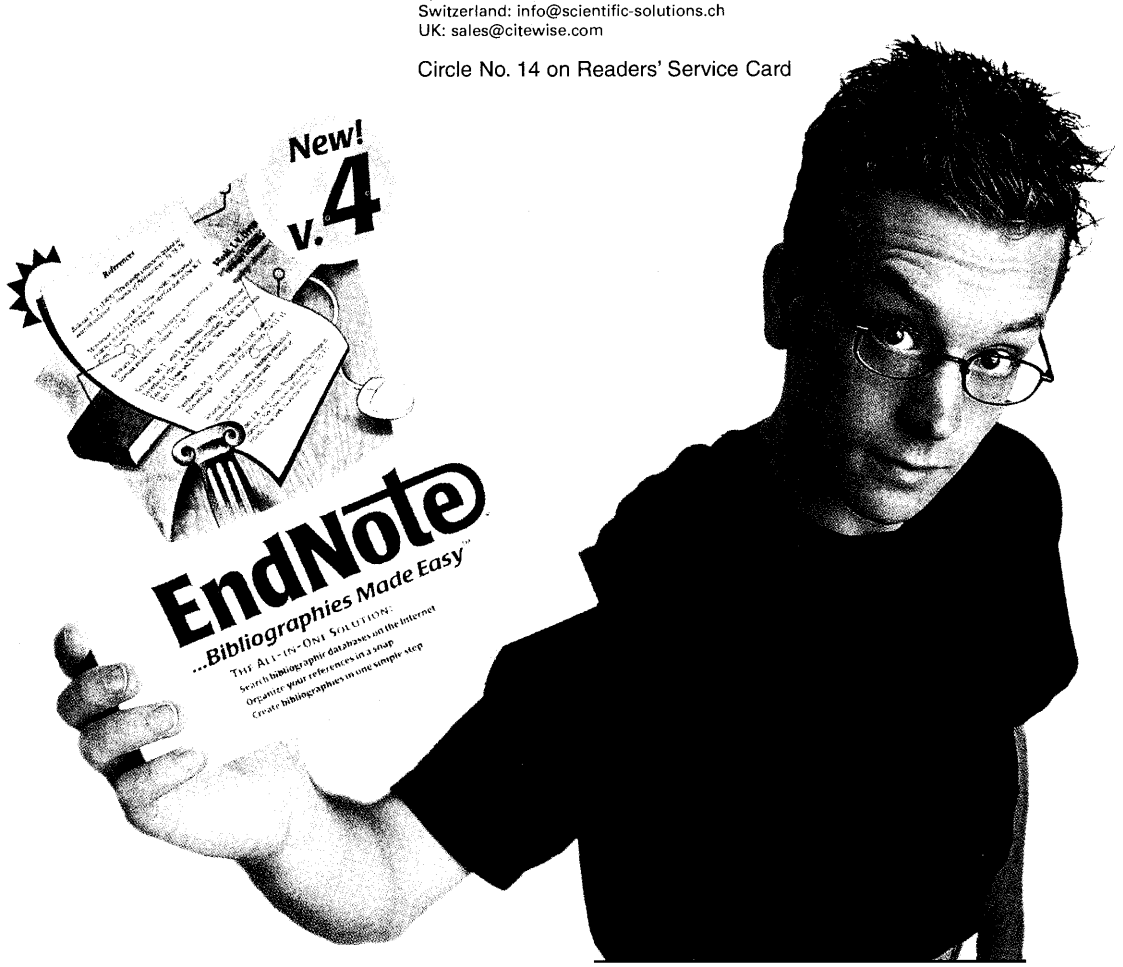

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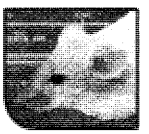

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* For the purpose of this prize, molecular biology is defined as "that part of biology which attempts to interpret biological events in terms of the physico-chemical properties of molecules in a cell" (McGraw-Hill Dictionary of Scientific and Technical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

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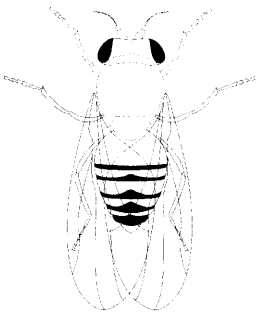
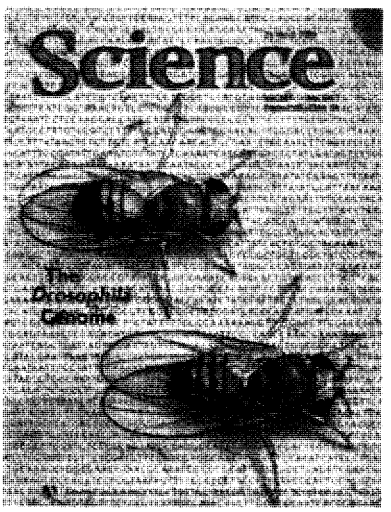
Little fly, big research.



Drosophila melanogaster
~ 180 million base pairs;
~14,000 genes



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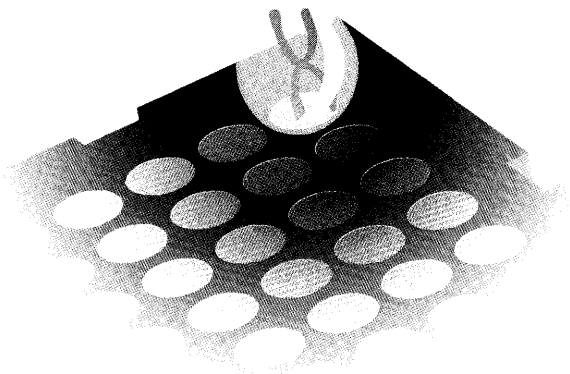

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*Ledford, M., et al., J. Molec. Diagnostics 2, 97-104 (2000); Hessner, M., et al, Clin. Chem. 46:8 1051-1056 (2000).

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