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7 December 2001

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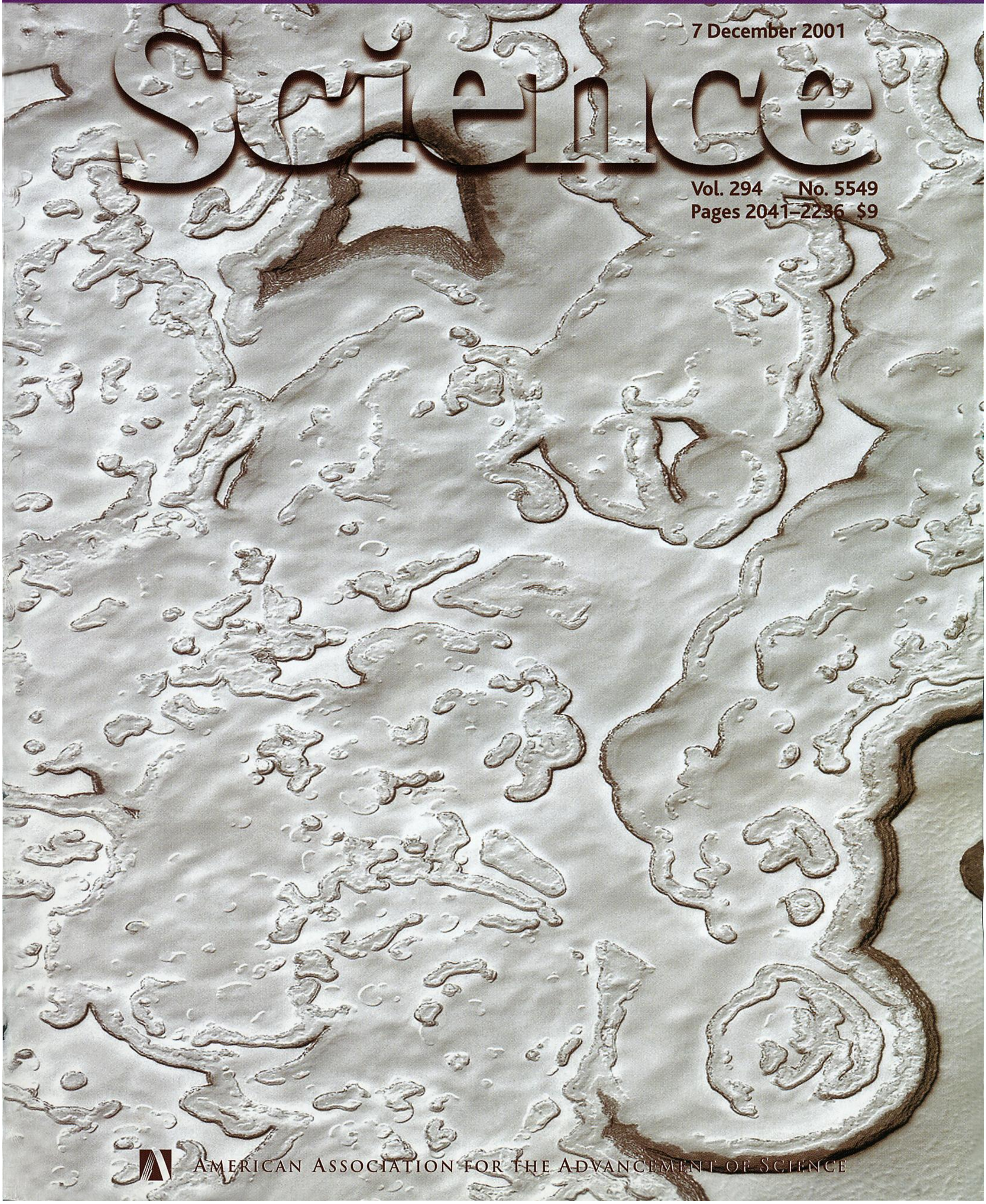

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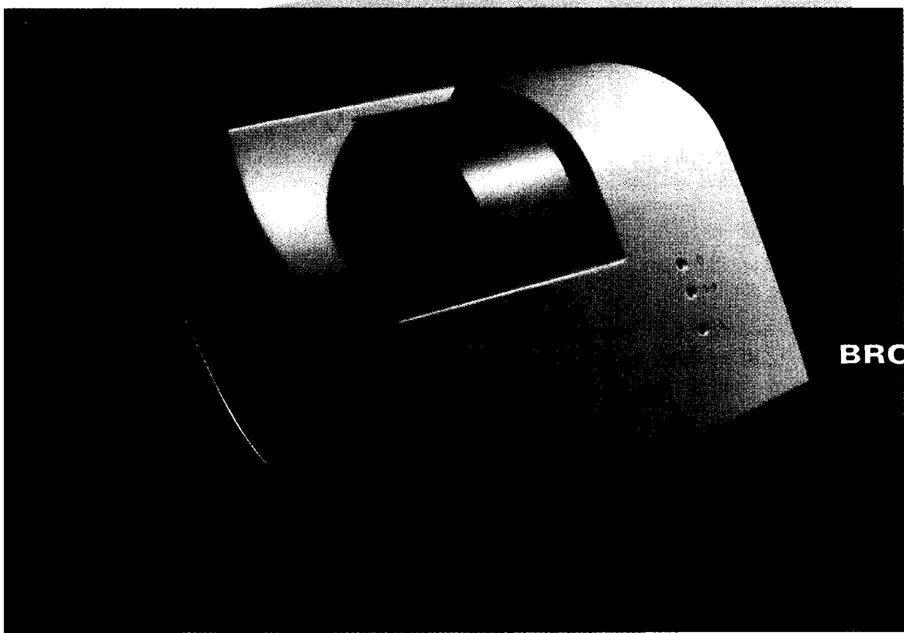

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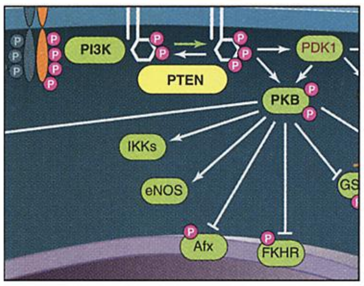
Volume 294 7 December 2001 Number 5549

NEWS

2074
Who will own the proteome?

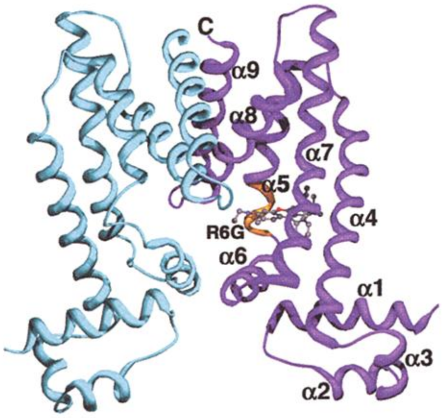
SCIENCE'S COMPASS



2116
PTEN—not just another tumor suppressor

RESEARCH

RESEARCH ARTICLES

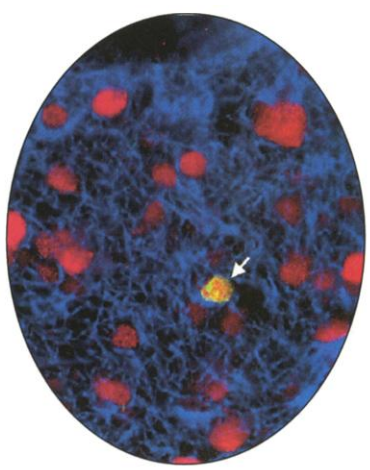


2158
Multidrug binding

REPORTS

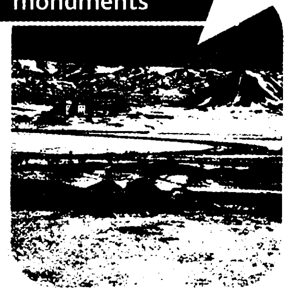
COVER 2146

A Mars Orbiter Camera image from 23 February 2000. Meter-scale changes detected in the course of a martian year in the pits and mesas of the perennial south polar cap suggest that it mostly consists of CO_2 ice. These findings indicate that significant climate change is occurring on Mars. [Image M12-02295: NASA, Jet Propulsion Laboratory, and Malin Space Science Systems; 87°S, 341.5°W; width 2.8 km, north toward left, sunlight from lower right and 20° elevation]



2127
Analysis of cell proliferation in the brain

New on *Science* Express Dating ancient monuments



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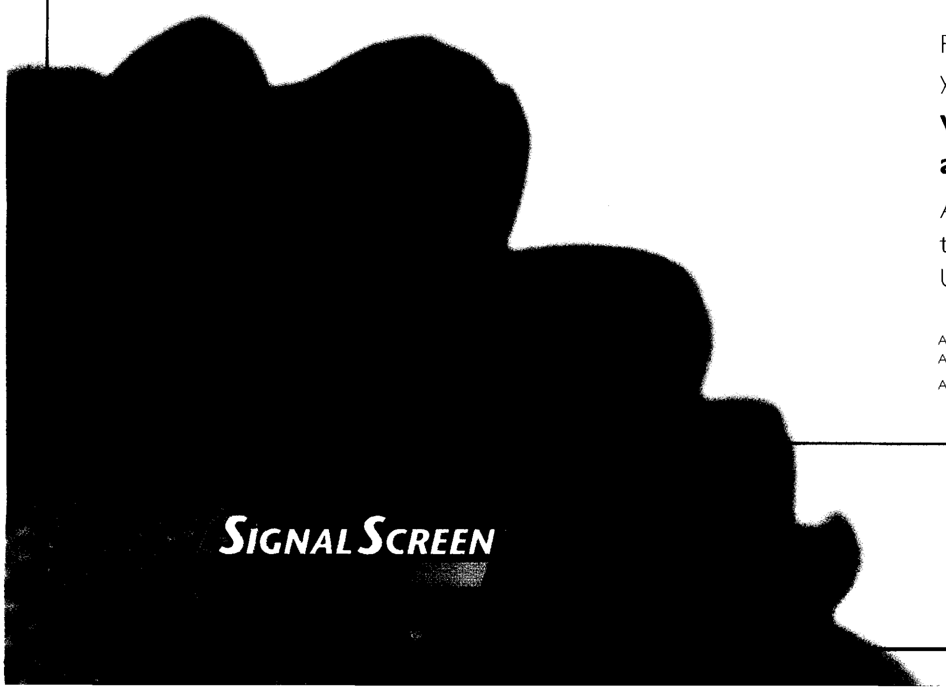

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CONTENT HIGHLIGHTS AS OF 7 DECEMBER 2001

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SCIENCE EXPRESS www.sciencexpress.org

Regional $^{14}CO_2$ Offsets in the Troposphere: Magnitude, Mechanisms, and Consequences B. Kromer, S. W. Manning, P. I. Kuniholm, M. W. Newton, M. Spurk, I. Levin

Anatolian Tree Rings and a New Chronology for the East Mediterranean Bronze-Iron Ages S. W. Manning, B. Kromer, P. I. Kuniholm, M. W. Newton

PERSPECTIVE: **A New Twist in the Radiocarbon Tale** P. J. Reimer

Rapid changes in atmospheric ^{14}C production rates can produce small but important regional differences in the apparent radiocarbon ages of mid-latitude trees—an understanding of which allows a new chronology for third- to first-millennium B.C. Anatolian tree rings.

CTCF, a Candidate Trans-Acting Factor for X-Inactivation Choice W. Chao, K. D. Huynh, R. J. Spencer, L. S. Davidow, J. T. Lee

The transcriptional regulator CTCF may be the long-sought trans-acting factor controlling X chromosome inactivation in mammals.

TECHNICAL COMMENTS

Crustaceans and the "Cambrian Explosion"

Siveter *et al.* (Reports, 20 July 2001, p. 479) described fossils of a phosphatocopid arthropod from Lower Cambrian strata in Shropshire, England, that provide "evidence for the occurrence of Crustacea, including Eucrustacea, in the Early Cambrian" and support "the hypothesis . . . of a late Precambrian history for the Metazoa." Fortey (Perspectives, 20 July 2001, p. 438) noted that the work raises doubts about the suddenness and rapidity of the Cambrian evolutionary "explosion." Budd *et al.*, in a comment, raise questions about some of the phylogenetic relationships proposed by Siveter *et al.*, and point out that the fossils "postdate the base of the Cambrian by some 32 million years . . . well beyond the range appropriate for testing Cambrian Explosion hypotheses." Siveter *et al.* offer a defense of their taxonomy. They also note that their fossil is "at most a few million years younger" than the age during which the "Cambrian evolutionary radiation achieved its 'explosive' character"—and that their analysis, coupled with evidence from other fossil assemblages, suggests a much earlier origin for the arthropod evolutionary line.

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/294/5549/2047a

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career resources for scientists

Global Feature: Careers in Science Broadcasting Edited by Next Wave Staff

The love of science that sent many into the lab in the first place was often inspired by radio and TV programs. This month, we hear from scientists from around the world who have carved out niches in the broadcast media.

Europe: European Science Bytes Compiled by E. von Ruschkowski and K. Urquhart

The latest news on science careers and education in Europe.

US: Building Bridges Between the Lab and Your Next Career S. Kunjibettu and B. J. Doranz

A collaboration among the Penn School of Medicine, the Wharton Business School, and the Port of Technology, a biotech and information technology incubator, provides postdocs with "field experience" in the biotech industry.

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ATR Takes ATRIP to Fix Defects R. J. Davenport

Protein partners watch over the genome.

Transgenic Mice: Three Strains with Distinct Lesions in the ATM Gene A. A. Sadighi Akha

Rodent models of the DNA repair disorder ataxia telangiectasia.

science's stke www.stke.org

signal transduction knowledge environment

Review: Signals from Eph and Ephrin Proteins—A Developmental Toolkit A. W. Boyd and M. Lackmann

A bidirectional signaling complex that can mediate cell attraction and repulsion.

Review: VEGF Receptor Signal Transduction T. Matsumoto and L. Claesson-Welsh

How do VEGF receptors control vasculogenesis?

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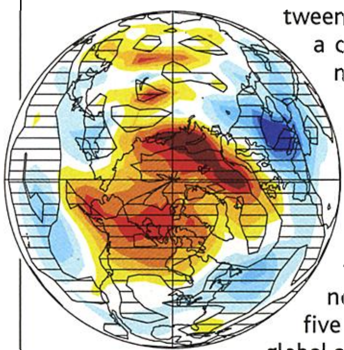
THIS WEEK IN Science

edited by Phil Szuromi

Solar Output and Climate Change

Changes in solar output, although relatively small, can apparently exert large effects on climate (see the Perspective by Haigh). Periodic episodes of surface-water cooling accompanied by increases in iceberg formation and transport have recurred in the North Atlantic throughout the last 100,000 years. Bond *et al.* (p. 2130 ✗; see the 16 November news story by Kerr) now show that virtually all of the centennial-scale expansions of cooler surface waters in the North Atlantic during the past 12,000 years were tied to decreases in the production of the cosmogenic nuclides ^{14}C and ^{10}Be. This finding strongly links these events to changes in solar irradiance and indicate that mechanisms to amplify small variations in solar forcing must exist. Between the mid-1600s and the early 1700s, when global average surface temperatures were generally among the lowest of the last millennium, there was a minimum in solar irradiance called the Maunder Minimum. Shindell *et al.* (p. 2149) use a general circulation model to evaluate possible mechanisms for temperature differences between the Maunder Minimum and those of a century later, when solar output remained relatively high for several decades. Their reconstructions suggest that solar-forced climate change during the Maunder Minimum was a result of a reduction in the intensity of the Arctic Oscillation/North Atlantic Oscillation, and that regional cooling over the continents during winter was as much as five times greater than the decrease of global average temperatures.



2138 Single-Molecule Transistor

Although there are many proposals for implementing molecular electronics, three-terminal devices such as transistors are one of the most promising architectures. Molecular transistors have been recently demonstrated using many thousands of molecules in a single monolayer, Schön *et al.* (p. 2138) now demonstrate switching confined to single molecules, which addresses the challenges of reducing energy dissipation and enabling large-scale integration. ✗

Carbon Dioxide Cycles on Mars

As Mars turns in its orbit around the Sun, seasonal changes at different latitudes are driven by the exchange of CO_2 between the atmosphere and the ice caps (see the Perspective by Paige). Smith *et al.* (p. 2141) used changes in elevation measured by the Mars Orbiter Laser Altimeter and Doppler tracking, both from the Mars Global Surveyor (MGS) spacecraft, to track the variation in CO_2 snow depth at different latitudes as each polar cap sublimates CO_2 in its summer season for transport to the opposite hemisphere, where it recondenses as snow. Malin *et al.* (p. 2146; see the cover) used images of the south polar cap, collected over a martian year by the Mars Orbiter Camera onboard MGS to measure the retreat of escarpments in the ice. The inferred rate of CO_2 sublimation was greater than expected and suggests that Mars may be in the midst of a major global climate change in which the polar caps are losing mass to the atmosphere.

Shell Games

The depth of the lysocline, where the transition between preservation and dissolution of sedimentary calcium carbonate occurs, differs between the major ocean basins. Its location depends partly on carbonate ion concentration and thus is a sensitive indicator of ocean circulation. Broecker and Clark (p. 2152; see the Perspective by Archer and Martin) report measurements of shell weights of selected populations of foraminifera which show that during the Last Glacial Maximum, the Pacific lysocline was deeper and the Atlantic lysocline was shallower than today, and that both oceans exhibited large carbonate concentration gradients as a function of depth, unlike at the present. The greater contrast between the carbonate ion concentration in deep waters produced in the northern Atlantic and those in the Pacific compared to the present, reflects major differences in thermohaline circulation.

No New Neocortical Neurons

Indications that cells in the adult primate's brain might proliferate to form new neurons have stood in stark contrast with previous studies which found that neurons of the central nervous system leave their mitotic phase during development. Kornack and Rakic (p. 2127) used the indicator bromodeoxyuridine to identify proliferating cells in the brains of adult macaque monkeys. Dividing cells found in the neocortex were identified as nonneuronal supporting cells; proliferation of neurons was limited to the hippocampus and olfactory bulb. Thus, whereas certain types of new cells may indeed be found in the adult brain, the contribution of these cells to complex neuronal functions may be only secondary.

A Model of Portliness

Individuals with visceral (intra-abdominal) obesity are particularly prone to develop a cluster of metabolic disturbances, termed "metabolic syndrome," that include glucose intolerance, insulin resistance, plasma lipid disorders, and hypertension. Because visceral obesity has been associated with high levels of glucocorticoids, Masuzaki *et al.* (p. 2166; see the news story by Gura) studied the role of 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1), an enzyme that can amplify glucocorticoid action and is overexpressed in the adipose tissue of obese humans. Transgenic mice that modestly overexpressed 11β HSD-1 in adipose tissue developed visceral obesity and, remarkably, displayed many of the defining features of the metabolic syndrome.

Taking on Drug Resistance

The *Staphylococcus aureus* protein QacR represses transcription of the *qacA* multidrug transporter gene. QacR also binds diverse cationic lipophilic drugs, and drug binding induces expression of

CONTINUED ON PAGE 2051

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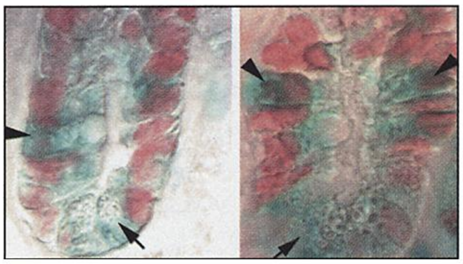
Aventis Pharma AG, Frankfurt am Main (Germany) www.aventis.com the *qacA* gene. Schumacher *et al.* (p. 2158) have determined the structures of six QacR-drug complexes. Drug binding causes a conformational change, relative to DNA-bound QacR, that causes induction and creates an extended multidrug-binding pocket. The bacterium *Streptococcus pneumoniae*, the major cause of the ear infection acute otitis media and more seriously of meningitis, pneumonia, and lethal sepsis, is present in an asymptomatic carrier state in the respiratory tracts of many children. This reservoir can pass drug-resistant strains to susceptible individuals. Loeffler *et al.* (p. 2170) have built upon technology developed against *S. aureus* in which a lytic enzyme was used to kill bacteria in the respiratory tract. In a mouse model of nasal infection, 1400 units of the enzyme Pal, an amidase from phage Dp-1, applied into the nose and mouth eliminated the bacteria. This treatment should not affect other bacteria, and resistant bacteria did not appear after extensive enzyme exposure.

Gut-Level Consequences

The epithelium of the mouse small intestine contains secretory three cell types (the goblet cells, enteroendocrine cells, and Paneth cells) and absorptive enterocytes. Yang *et al.* (p. 2155; see the Perspective by van den Brink *et al.*) examined whether the factor *Math1*, which is found in the intestine and reported to be necessary for cell fate determination in the central nervous system, is involved in gut cell determination. In mice that lack functional *Math1*, the secretory cells failed to differentiate and the progenitors remained in the proliferating stage. However, the loss of *Math1* did not affect the enterocytes.



Getting Used to a Smell

In vertebrate olfactory neurons, odor molecules stimulate the opening of cyclic nucleotide–gated channels (CNGs). The resulting influx of Ca^{2+} ions also triggers a negative-feedback mechanism in which channel activity is inhibited when bound to a Ca^{2+}-calmodulin (CaM) complex. This mechanism promotes olfactory adaptation and allows animals to continually evaluate the odor environment. Two groups have determined that two of the channel's three subunits are required for odor adaptation. Munger *et al.* (p. 2172) show that channels from mice lacking the CNGA4 subunit exhibited slower Ca^{2+}-CaM–mediated inhibition. Bradley *et al.* (p. 2176) have used a heterologous expression system to show that both the CNGA4 and CNGB1b subunits facilitate Ca^{2+}-CaM binding to the open state of channel.

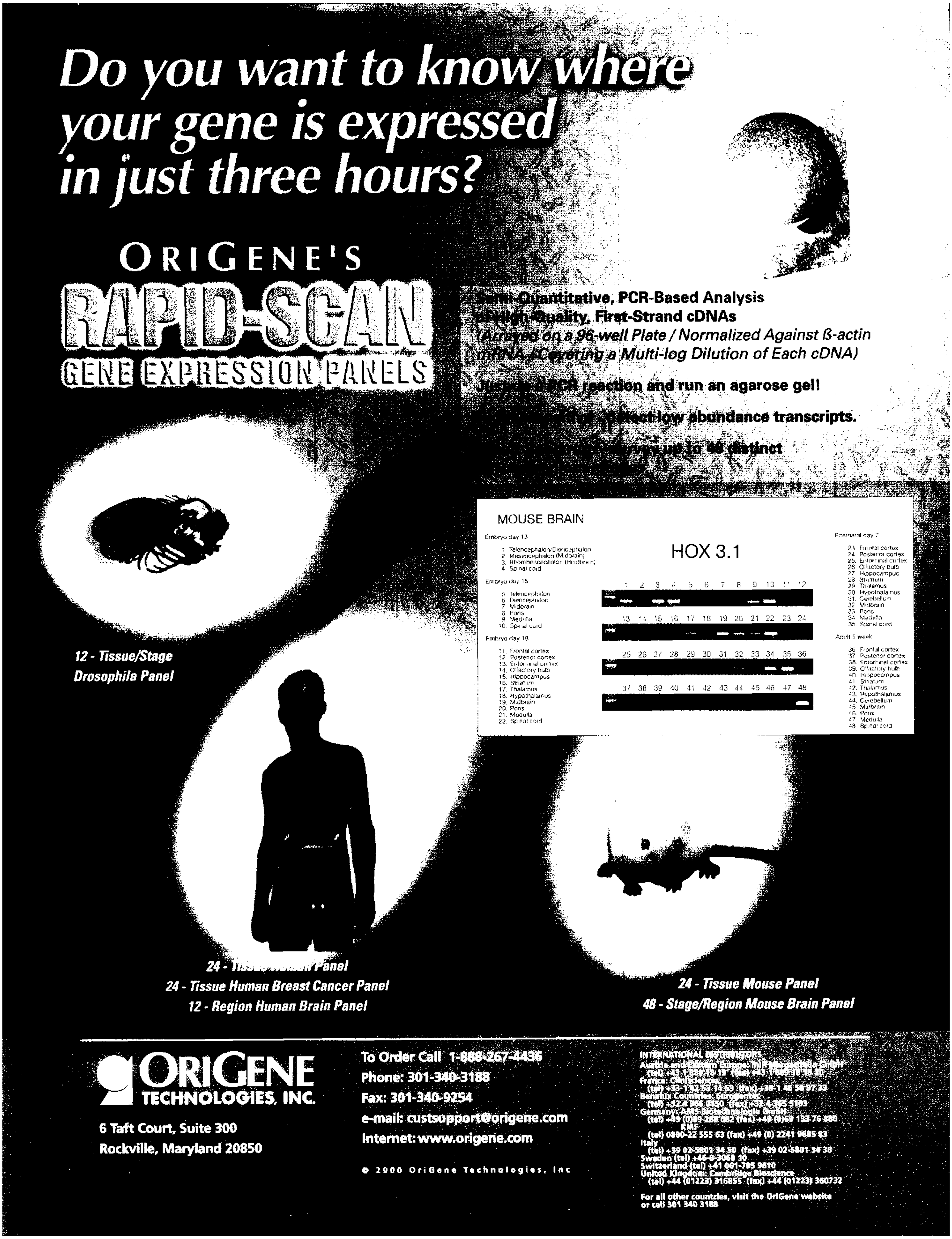
Cut and Run to the Nucleus

The conventional view of receptor tyrosine kinase–mediated signal transduction holds that upon ligand binding, a signaling cascade initiated at the cell surface ultimately regulates gene expression. Although it has been proposed that such receptors may localize to the nucleus to affect transcription directly, the mechanism for nuclear translocation has not been clear. Ni *et al.* (p. 2179; see the Perspective by Heldin and Ericsson) show that cleavage of ErbB-4, an epidermal growth factor receptor family member, by presenilin-dependent–secretase releases a transcriptionally active intracellular domain of ErbB-4 to the nucleus. In the absence of this cleavage, the ErbB-4 ligand could not modulate cell growth.

Bigger Is Not Better

The tumor suppressor gene *Pten* also plays a critical role for normal brain development. Standard *Pten* deletion mutants in mice are lethal in early development, so Groszer *et al.* (p. 2186; see the Perspective by Penniger and Woodgett) developed a conditional knockout that deletes PTEN in the central nervous system at mid-gestation. These mice showed hyperactivation of certain signal transduction pathways; they also exhibited enlarged brains with multiple malformations, and more and bigger neural cells. Analysis of cell proliferation and apoptosis in the mutant brains suggests that PTEN controls progression of neural progenitor cells through the cell cycle.

CREDIT: YANG *ET AL.*



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6. Diencephalon
7. Midbrain
8. Pons
9. Medulla
10. Spinal cord
Embryo day 18
11. Frontal cortex
12. Posterior cortex
13. Entorhinal cortex
14. Olfactory bulb
15. Hippocampus
16. Striatum
17. Thalamus
18. Hypothalamus
19. Midbrain
20. Pons
21. Medulla
22. Spinal cord
Postnatal day 7
23. Frontal cortex
24. Posterior cortex
25. Entorhinal cortex
26. Olfactory bulb
27. Hippocampus
28. Striatum
29. Thalamus
30. Hypothalamus
31. Cerebellum
32. Midbrain
33. Pons
34. Medulla
35. Spinal cord
Adult 5 week
36. Frontal cortex
37. Posterior cortex
38. Entorhinal cortex
39. Olfactory bulb
40. Hippocampus
41. Striatum
42. Thalamus
43. Hypothalamus
44. Cerebellum
45. Midbrain
46. Pons
47. Medulla
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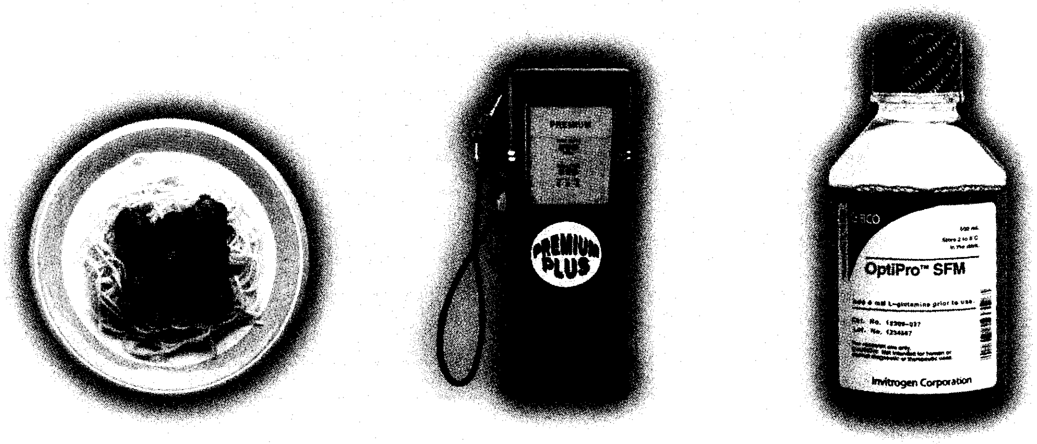

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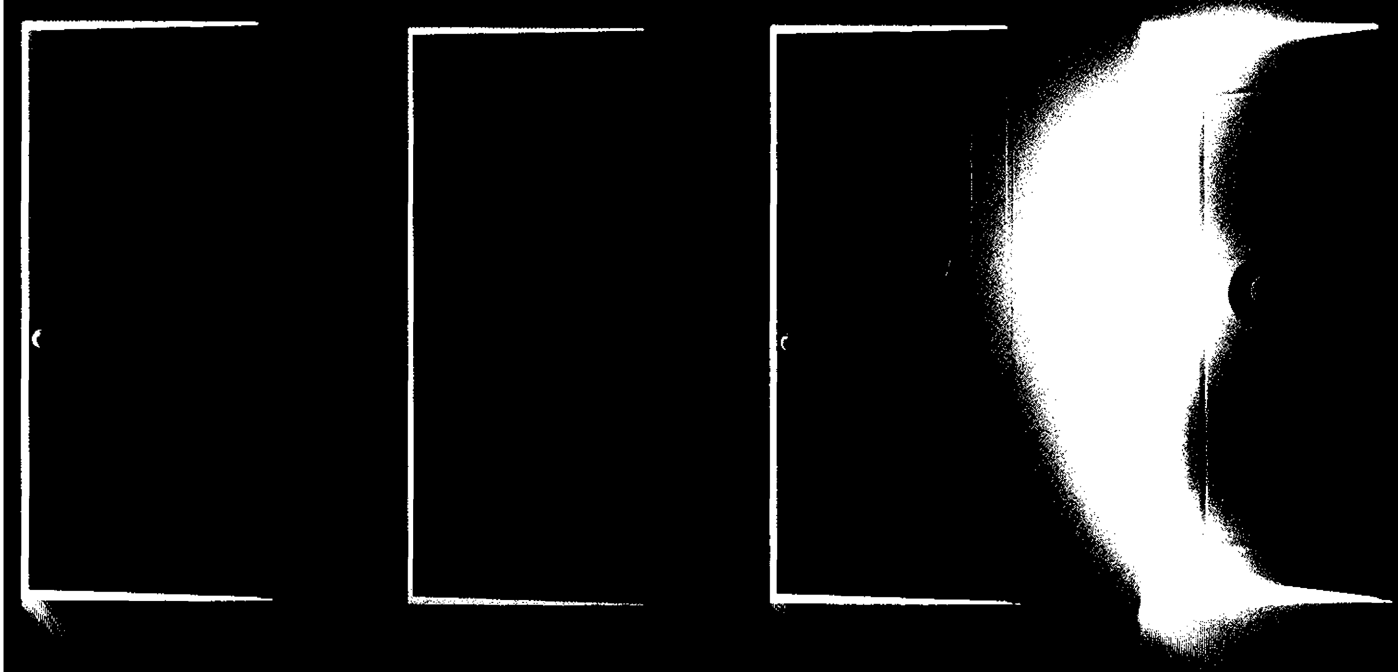

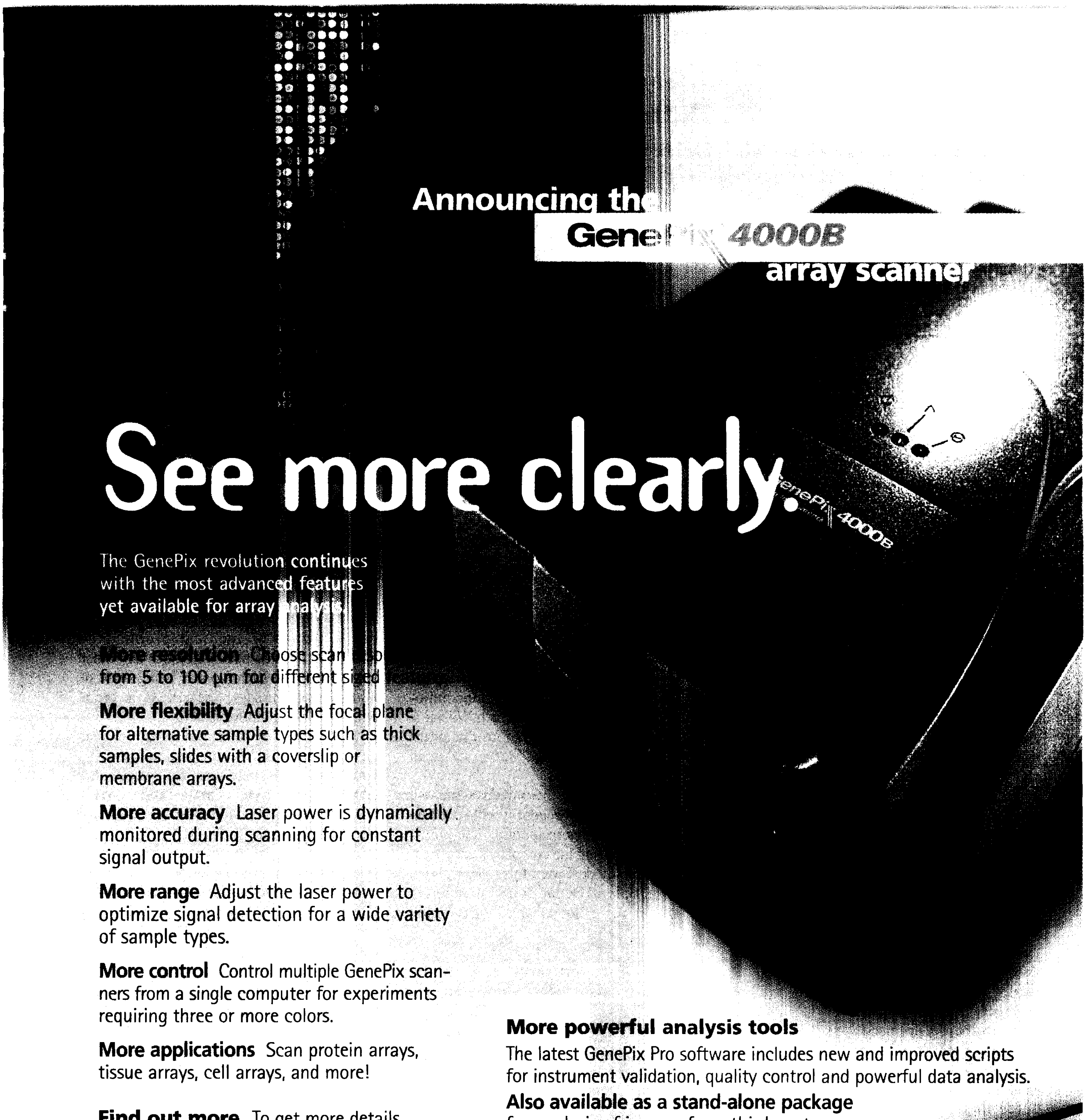
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We especially want to consider how to model conformational flexibility of component proteins in the process of fitting such maps. The presentations we have scheduled set the stage for the discussions during which we encourage participants to bring out their results and ideas.

Organizing committee: Axel Brunger (Stanford University), David DeRosier (Brandeis University), Stephen Harrison (Harvard University), and Eva Nogales (University of California at Berkeley).

The Program

Session I. The State of Structural Biology of Large Structures. Moderator Helen Saibil

- The power of electron cryomicroscopy. *Richard Henderson*
- The ribosome – a molecular machine in motion. *Joachim Frank*
- Biochemical basis for x-ray crystallography of the ribosome. *Jamie Cate*

Session II. Extending X-ray Crystallography to Ever Larger Structures. Moderator Keith Hodgson

- Can we routinely collect useful data from micro-crystals? *Andy Thompson*
- Future x-ray sources. *Janos Hajdu*
- The phase problem: does size matter? *Randy Reed*

Session III. New Ways to Obtain Large Complexes for Structural Studies. Moderator Axel Brunger

- Stabilizing multi-component biological complexes for structural studies by protein engineering, expression, and refolding – AND – avoiding artifacts. *Don Wiley*
- Expression and co-expression of components. *Speaker to be announced.*

Session IV. What Does the Future Hold for Electron Cryomicroscopy? Moderator Bob Glaeser

- Single particles always fit the mold. *Niko Grigorieff*
- The hybrid approach to electron crystallography. *Ken Downing*
- Electron tomography: Towards visualizing macromolecular assemblies inside cells. *Wolfgang Baumeister*
- Polymorphism, can we detect it? Can we use it? Can we control it? Examples from actin and nucleoprotein complexes. *Ed Egelman*

Session V. Can Hybrid Methods Provide Credible Atomic Models? Moderator Eva Nogales

- Atomic model of the cell: docking in a tomographic environment. *Niels Volkmann*
- Reconciling shape with structure: Morphometric strategies for multi-resolution flexing. *Willy Wriggers*

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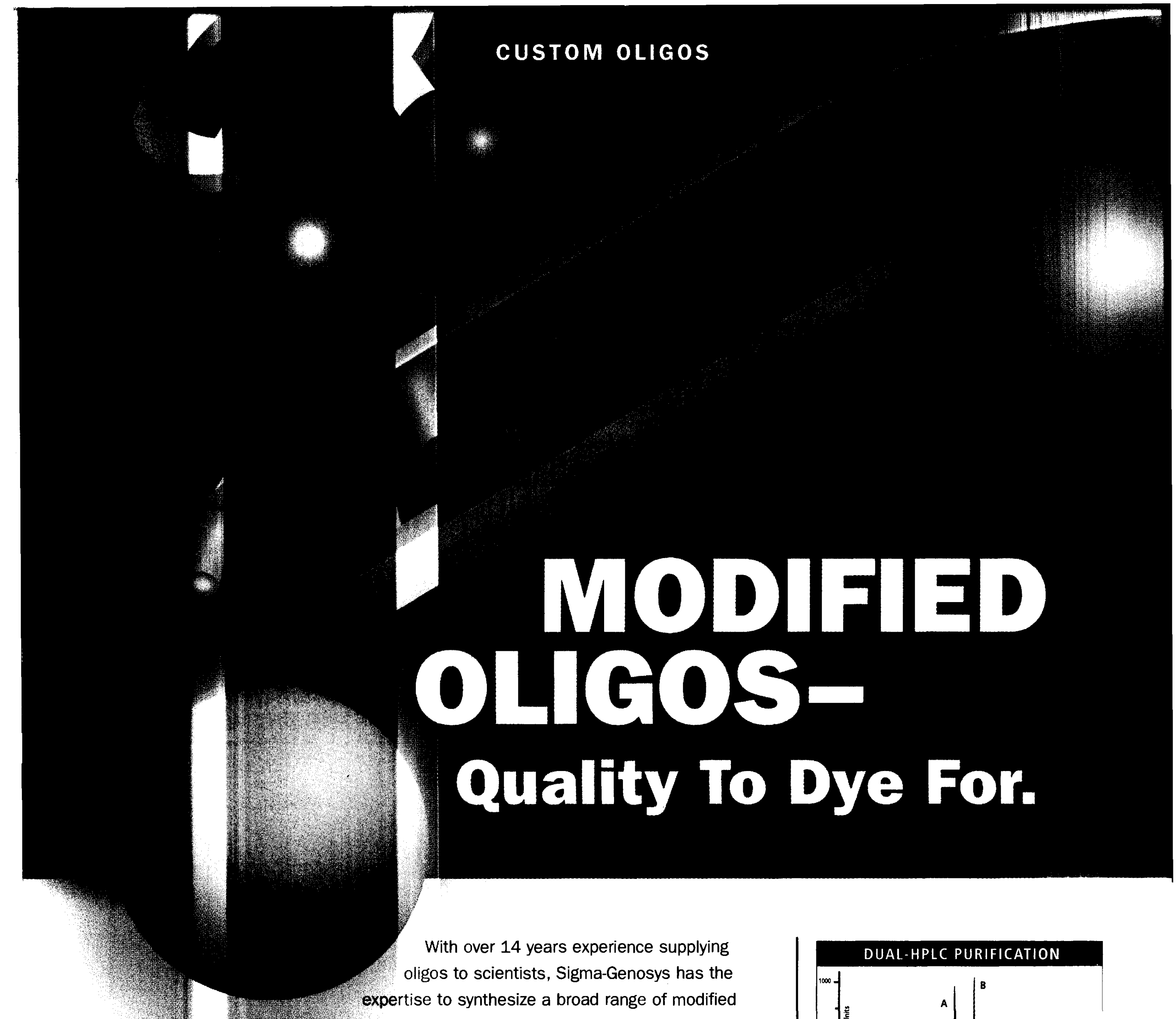

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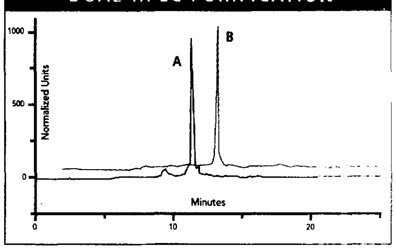

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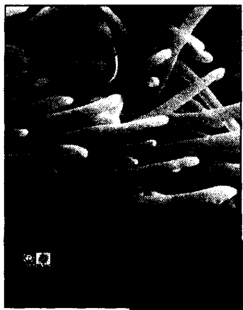

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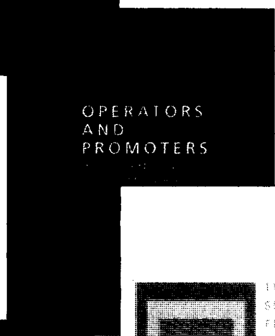

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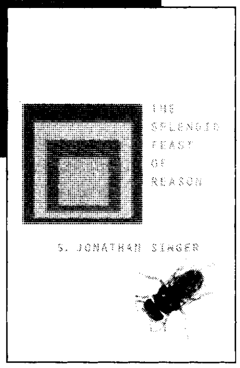

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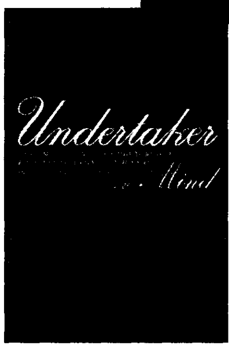

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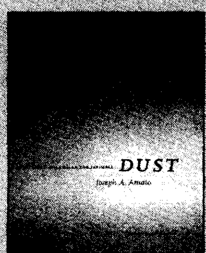

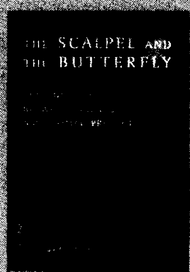

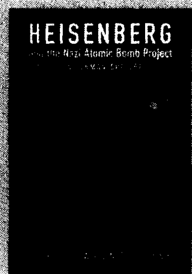

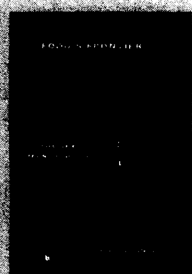


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