22 December 2000

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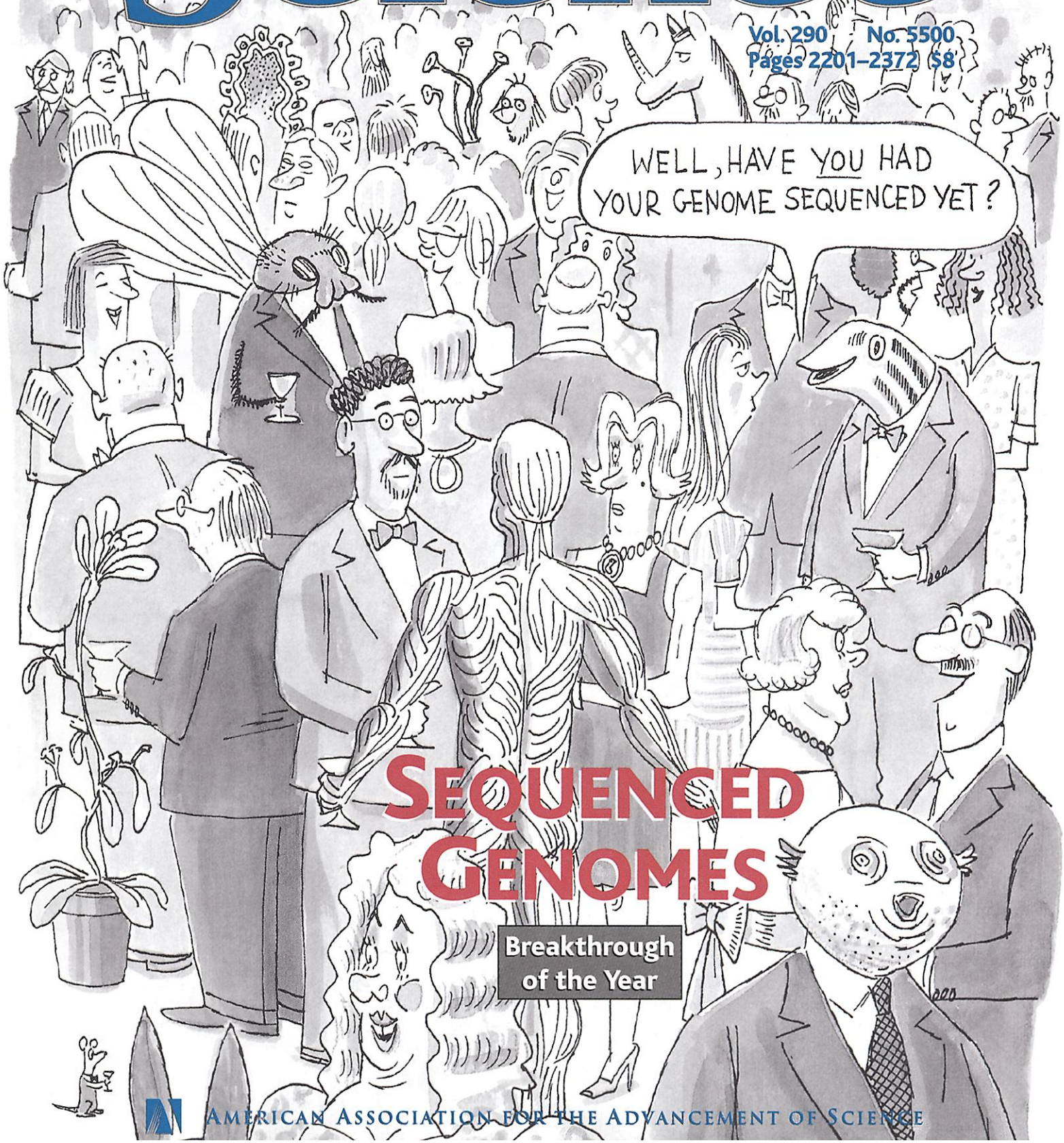

SEQUENCED GENOMES

Breakthrough of the Year

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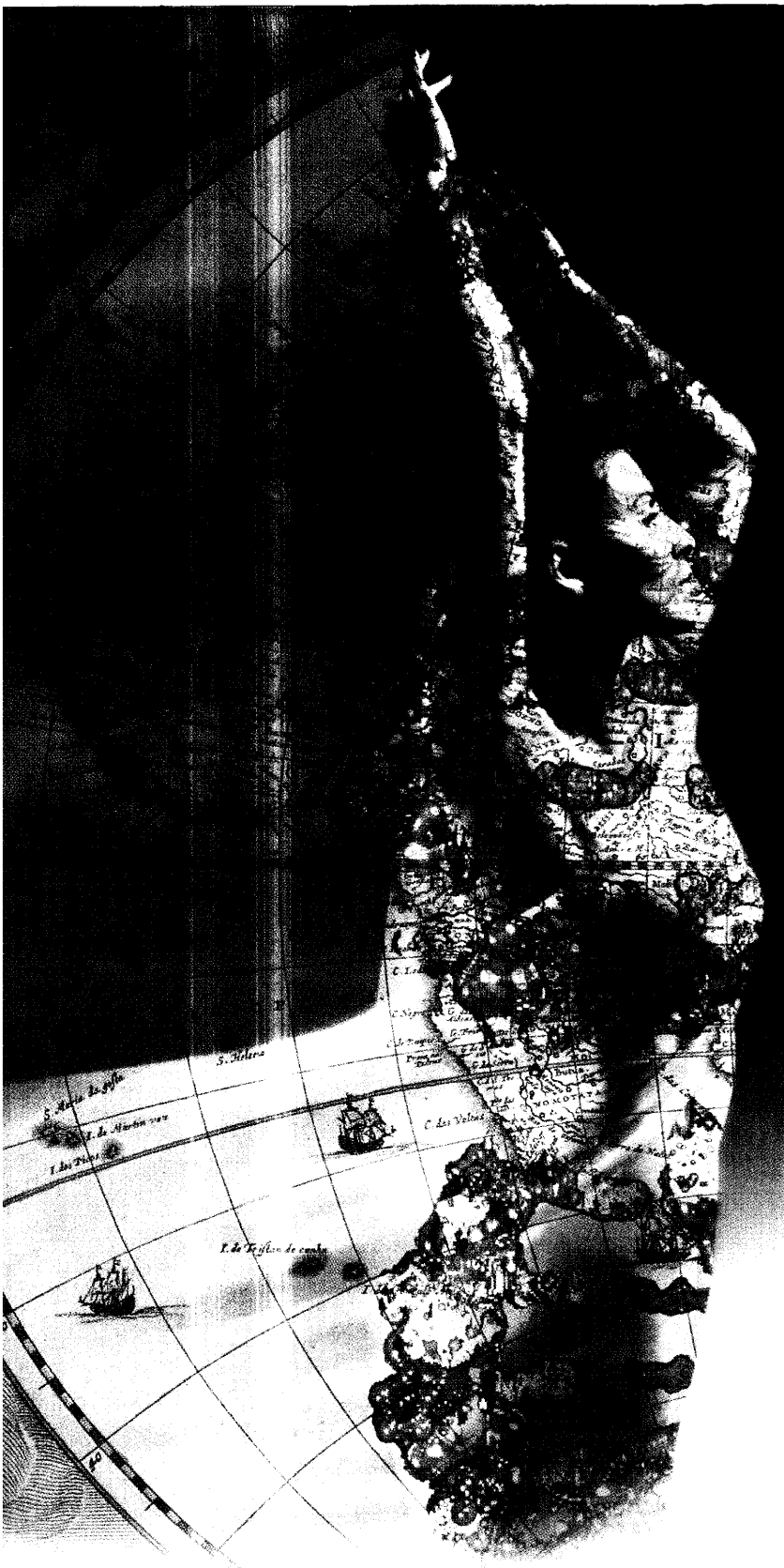

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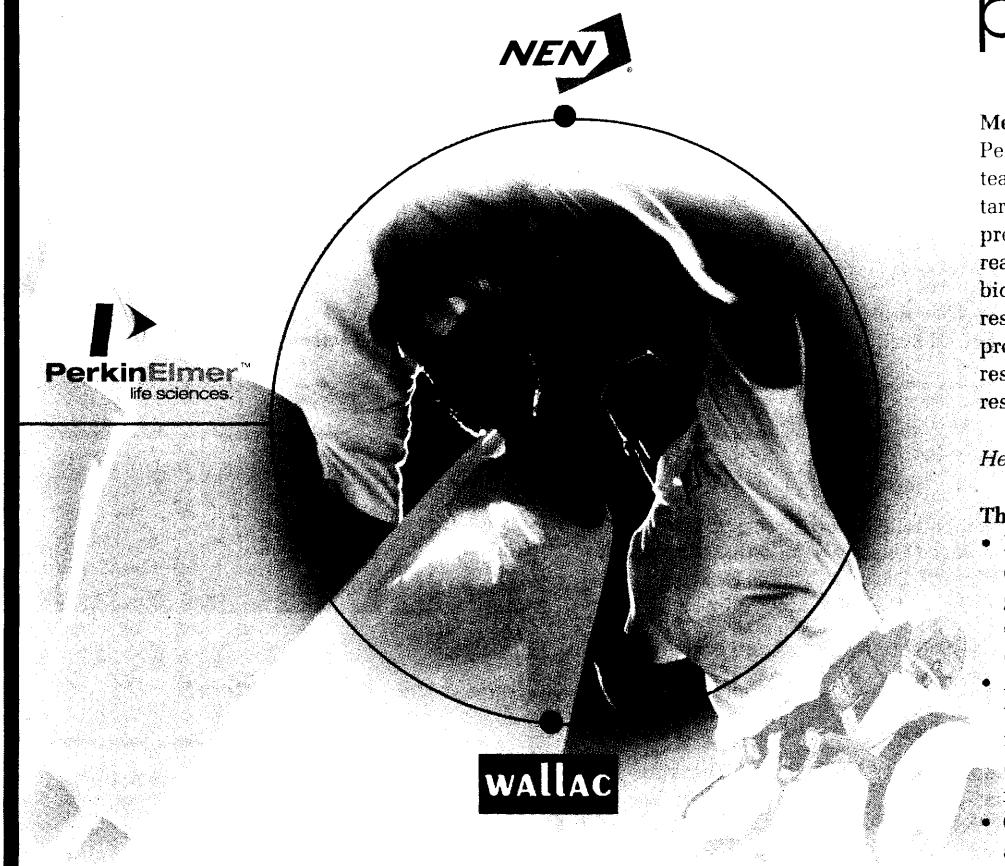

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VOLUME 290 22 DECEMBER 2000 NUMBER 5500

Science

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COVER Creatures great and small are having their genomes sequenced, as highlighted in this Breakthrough of the Year special issue. Now that genomics has come of age, the growing library of gene sequence data is opening a new era of sophisticated genetics research. See the Breakthrough of the Year special section, beginning on page 2220, and the Editorial on page 2255. [Illustration: Peter Steiner]

2236
President Clinton on science

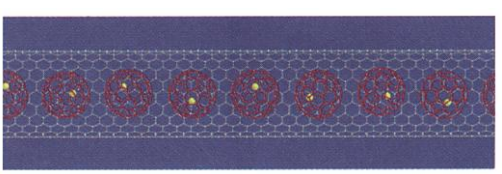
NEWS

NEWS OF THE WEEK

NEWS FOCUS

RESEARCH

REPORTS



2280
Where is the gadolinium atom?

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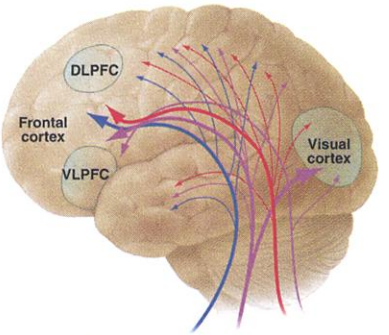
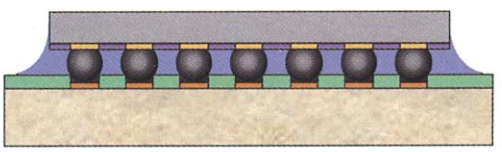


2275
Pathways to short-term memory



2269
Better packaging for chips

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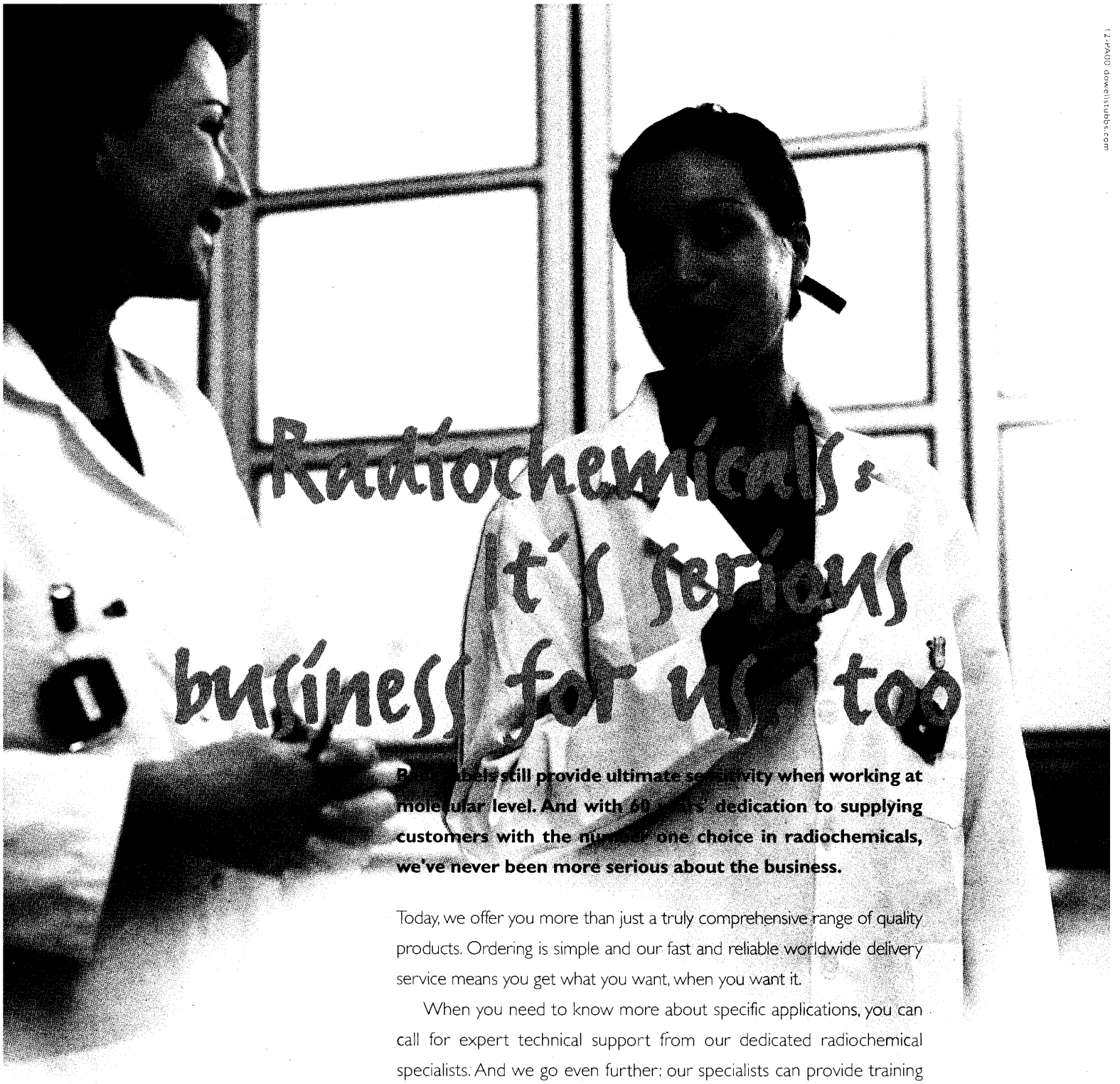

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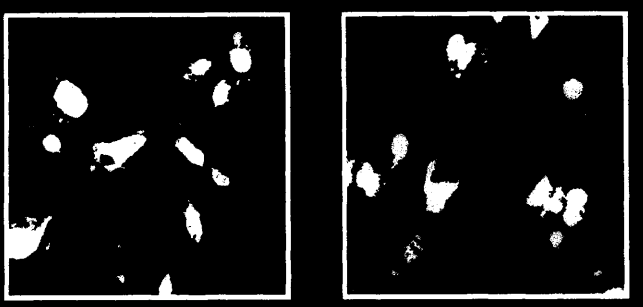
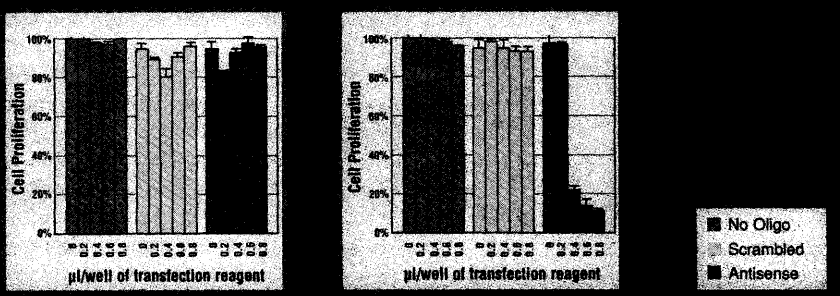


It may fluoresce, but does it function?



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TOWARD SILICON-BASED OPTOELECTRONICS

Silicon dominates semiconductor microelectronics, but the fabrication of silicon-based optical devices, which would allow for a seamless and fully integrated optoelectronics technology, is still challenging. The indirect band gap of silicon, a property shared with other group IV elements such as germanium, has presented a considerable barrier to its use in optical applications (and other materials) such as GaAs, are typically used instead. Using a quantum-cascade design that involves a series of coupled and carefully deposited Si and SiGe quantum wells, Dehlinger *et al.* (p. 2277) demonstrate electroluminescent behavior from such a structure. This single-band design overcomes the limitations of indirect gap materials.

SINGLE PHOTONS ON DEMAND

For the successful implementation of quantum cryptography, a light source capable of reliably producing at most a single photon per pulse is a key requirement. Previous work has shown that photon emission from a nonlinear radiator, such as a single molecule or a quantum dot, shows antibunching behavior. However, antibunching is not a sufficient condition to produce single photons, and further mechanisms are required to ensure single photons on demand. Michler *et al.* (p. 2282; see the Perspective by Benjamin) present one such mechanism involving the excitation of an InAs quantum dot embedded in a microdisk cavity with pulsed laser light. The subsequent relaxation pathway of the quantum dot is such that the emission of a single photon per excitation pulse is ensured.

PICKED OUT OF A LINEUP

Electron energy loss spectroscopy (EELS) can provide chemical fingerprints of specific elements in a sample without the need for the atoms to be present in the topmost surface layer, as would be the case for scanning probe techniques. Suenaga *et al.* (p. 2280) now show that spatial resolution rivaling that of scanning probe and electron microscopy techniques can be obtained in EELS. They can identify gadolinium (Gd) atoms, which were encapsulated in fullerenes that were then aligned within a single-wall carbon nanotube. Individual Gd atoms, which are spaced about a nanometer apart in this environment, can be identified.

ATLANTIC COOLING

During the past several million years, Earth's climate has cooled significantly. This cooling may have been the result of a change in the ocean's large-scale circulation caused by the closure of the Central American Seaway. The blocking by the Isthmus of Panama began to affect deep ocean circulation 4.5 million years ago and was essentially complete in another 1 to 2 million years. Marlow *et al.* (p. 2288) present a 4.5-million-year record of sea surface temperature off the coast of southwest Africa, which shows that temperatures there have decreased by an extraordinary 10°C during the past 3.2 million years. This drop is thought to be the result of a combination of global cooling, increased wind-driven upwelling, and a radical change of surface Atlantic Ocean circulation.

AN ARID AMAZON?

Reconstructing the precipitation history of the Amazon Basin since the last glacial period is important for evaluating claims that arid conditions reduced or fragmented the rainforests, for constraining the role of the tropics in the budget of atmospheric methane, and for understanding how tropical climate may have affected the global water cycle (see the Perspective by Betancourt). Maslin *et al.* (p. 2285) have taken an obvious but previously unused approach to clarify this vigorously debated issue. By measuring the calcite oxygen isotopic composition of surface-dwelling foraminifera, they capitalize on the isotopic difference between freshwater and ocean water to determine how much discharge has flowed from the Amazon River and mixed with the ocean just downstream of the river's mouth during the past 14,000 years. Their results show that the Younger Dryas was extremely dry, and that the present period is the wettest time in the record. In a separate study, Mayle *et al.* (p. 2291) use pollen analysis to examine the long-term dynamics of forest-savanna boundaries in southern Amazonia, which depend intimately on climate patterns. Consistent with the results of Maslin *et al.*, they find that the present southern boundary of forest in Bolivia represents the greatest southern extent of forest for the past 50,000 years, and that the forest at its southern limit may be less than 3000 years old.

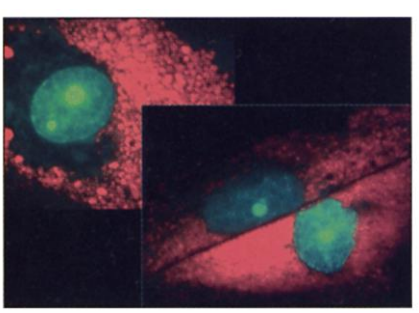
A HOTSPOT FOR AD GENES

The principal genes that are mutated in the rare, early onset familial form of Alzheimer's disease (AD) were identified and characterized some time ago. Howev-

CONTINUED ON PAGE 2211

PROGRESS IN NIEMANN-PICK C DISEASE

Patients with Niemann-Pick C (NPC) disease have a genetic defect that causes excessive accumulation of cholesterol in the liver, spleen, and other vital organs. At the cellular level, the cholesterol becomes trapped in the endolysosomal compartment rather than being transported to the plasma membrane. In almost all patients, the disease is caused by disruption of a transmembrane protein, NPC1, whose precise function has remained elusive. Further insights into the relation of NPC1 to cholesterol transport are the subject of two reports (see the news story by Marx). Davies *et al.* (p. 2295) show that NPC1 has sequence and functional homology with a family of prokaryotic permeases called the resistance-nodulation-division (RND) proteins, which transport lipophilic drugs and other target molecules out of the bacterial cytosol. When expressed in *Escherichia coli*, NPC1 transported acriflavine and fatty acids, but not cholesterol, from the culture medium into the cytosol. These results suggest that NPC1 is a member of an ancient family of multidrug efflux pumps that in mammalian cells have assumed housekeeping functions in cellular cholesterol homeostasis. In independent work, Naureckiene *et al.* (p. 2298) show that a rare subset of NPC patients with normal NPC1 function have a genetically determined deficiency in HE1, a cholesterol-binding protein localized in the lysosomes. These findings may lead to a better understanding of the mechanisms regulating cholesterol transport.



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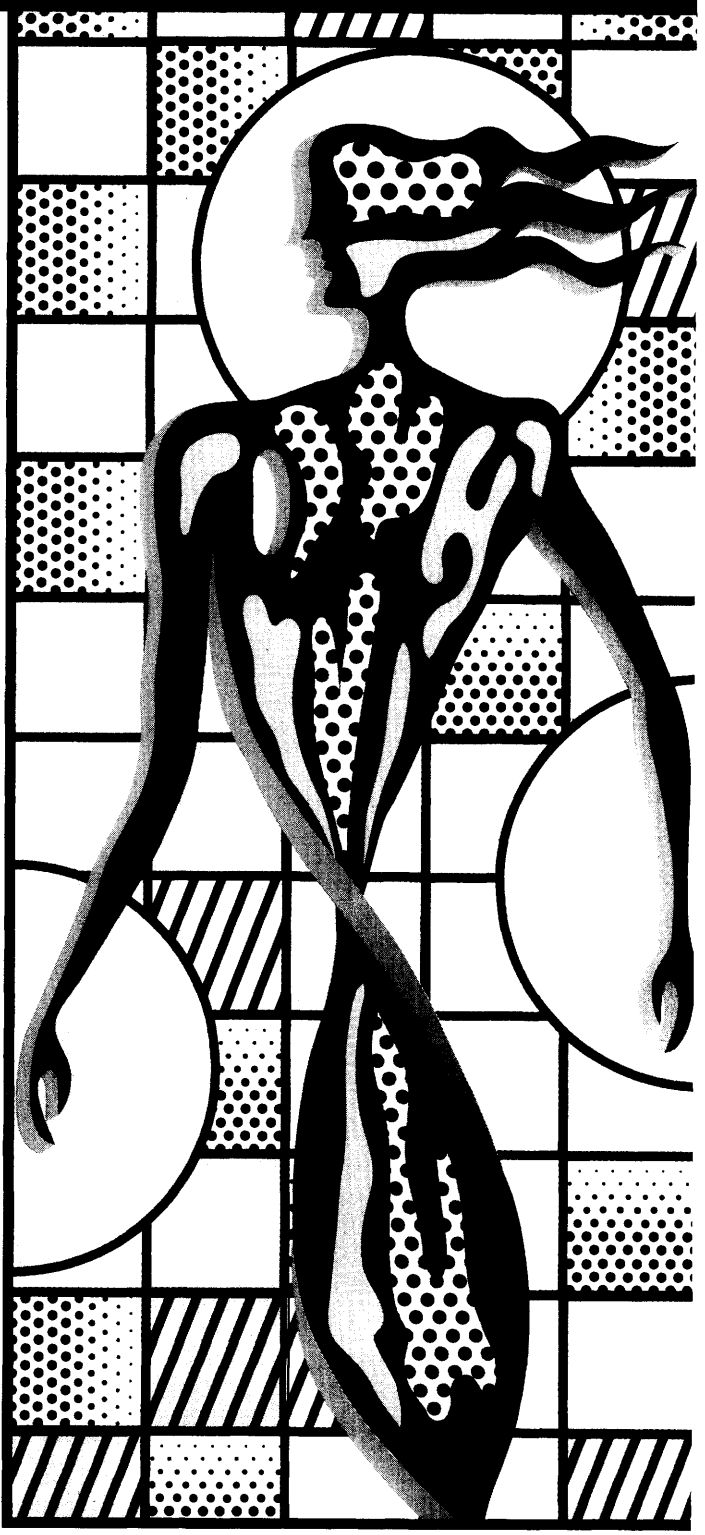

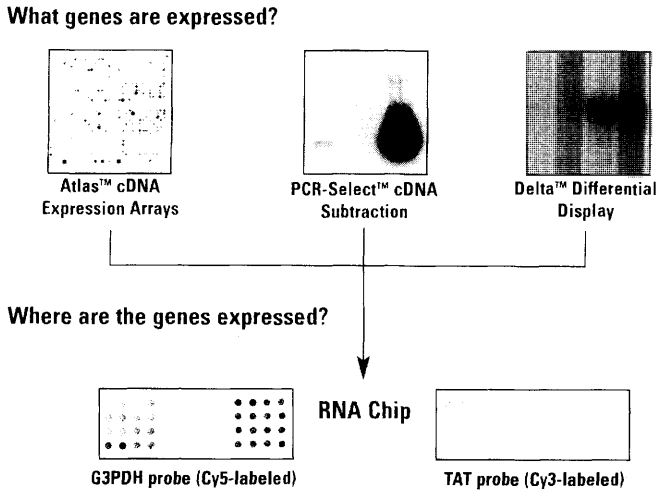

The RNA Chip™ links differential screening strategies with functional analysis. Using a cDNA array, cDNA subtraction, or differential screening, a gene can be identified to be up- or down-regulated in a sample. A probe made from that cDNA can be used to identify where the gene is expressed. In the example above, the gene was terminal aminoltransferase (TAT), which is shown to be active in the liver samples of the RNA Chip. G3PDH was used as a housekeeping control gene. The results were scanned with an Axon Gene Pix™ 4000 Array Scanner

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THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 2209

er, pinpointing genes associated with the more common, late onset form of AD has proved much more difficult. Three reports by Bertram *et al.* (p. 2302), Myers *et al.* (p. 2304), and Ertekin-Taner *et al.* (p. 2303) now present evidence from genetic linkage studies that highlight a hotspot on the longarm of human chromosome 10 that may contain one or more genes associated with late onset AD.

DIVIDER'S LICENSE

When eukaryotic cells divide, they must replicate their genome once and only once. A process known as licensing makes sure that cells must finish dividing before being allowed to replicate DNA again. In addition to the inhibition of further replication by cyclin-dependent kinases, geminin is thought to block the binding of mini-chromosome maintenance (MCM) complexes to the origins of replication. Wohlschlegel *et al.* (p. 2309; see the Perspective by Lygerou and Nurse) now show in human cells that geminin interacts with human homolog of Cdt1, a replication factor that was recently identified as being needed for MCM loading. Cdt1 is present in the G_1 and S phases, whereas geminin is present in the S and G_2 phases, thus suggesting that geminin helps prevent inappropriate firing of replication that might be induced by Cdt1.

MAINTAINING EARLY DEVELOPMENT

Although much is known about the transcription machinery for the three eukaryotic polymerases, relatively little is known about the role of the TATA-binding protein (TBP) or TBP-related factors in the early development of vertebrates. Veenstra *et al.* (p. 2312) have used antisense oligonucleotides to examine the role of TBP or the TBP-like factor (TLF) during early *Xenopus* embryogenesis. The two factors have different roles, in that TBP-deficient embryos undergo the initial phases of gastrulation but fail to complete subsequent stages of development, and TLF is required for the initiation of zygotic transcription. Hence, TBP and its related factor TLF are both necessary for *Xenopus* development, with each factor displaying different functions in early embryogenesis and transcription.

BINDING ASSAYS BY THE GENOME

In the cell, proteins bind to DNA elements to regulate such processes as transcription, replication, and chromosome condensation and cohesion. Many recent studies have tried to elucidate the various mechanisms involved in these processes, including specific protein-DNA interactions. For these analyses, researchers have widely used the techniques of chromatin immunoprecipitation analysis and DNA microarrays to examine protein-DNA interactions and gene expression levels, respectively. Ren *et al.* (p. 2306) have now combined these two methods to monitor in vivo protein-DNA interactions across the entire yeast genome. This genome-wide location analysis method was used to characterize two transcriptional activators Gal4 and Ste12. These techniques should allow for a more detailed understanding of global regulatory networks.

HOLD THOSE THOUGHTS

Working memory (the active representation of information in one's mind) is mediated by a widely distributed network of neuronal circuits in the brain. In a functional magnetic resonance imaging study, Furey *et al.* (p. 2315; see the Perspective by Robbins *et al.*) analyzed how the brain cholinergic system interacts with the different components of the central nervous system involved in a visual working memory task. During encoding of faces, a change in cholinergic activity induced by a drug that inhibits the breakdown of acetylcholine enhanced the selectivity of responses in the ventral occipital cortex and simultaneously reduced the activity in prefrontal regions. These results show how neurochemical processes regulate the neural systems involved in working memory function.

SIMPLIFYING SURFACES

In a variety of scientific disciplines, it is often desirable, although not always feasible, to transform high-dimensional data into a low-dimensional space. For example, the black-and-white image of a face contains light and dark areas whose appearance may depend on the direction of illumination. As the head is rotated, the mix of light and dark areas changes in a continuous but very complicated fashion because of the presence of discrete features, such as cheekbones and eyebrows. Nevertheless, there is an underlying simplicity defined by a single parameter—rotation. Tenenbaum and da Silva (p. 2319) and Roweis and Saul (p. 2223) present two algorithims that are able to compute this transformation, and the implications of being able to make this computation are discussed by Seung and Lee in a Perspective.

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Childhood deafness is one of the most frequent hereditary defects. Recently, teams of scientists have focused on a gene called CX26, where mutations have been linked to hearing impairment. To identify and characterize how genes like CX26 are involved in intercellular communication, life scientists use DNA linkage and sequencing systems from Applied Biosystems.

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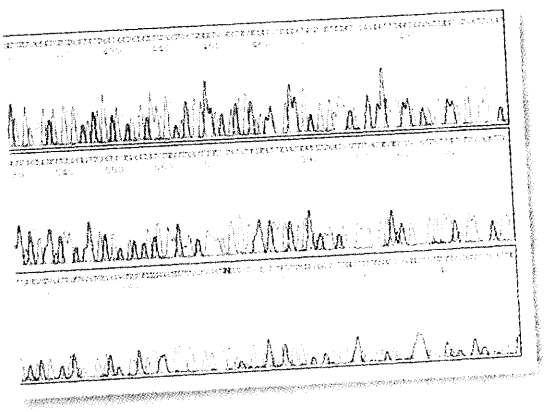

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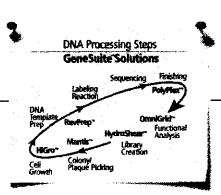

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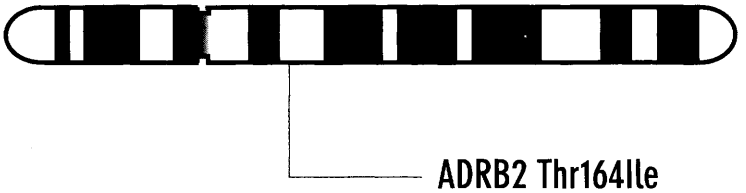

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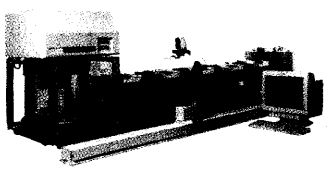

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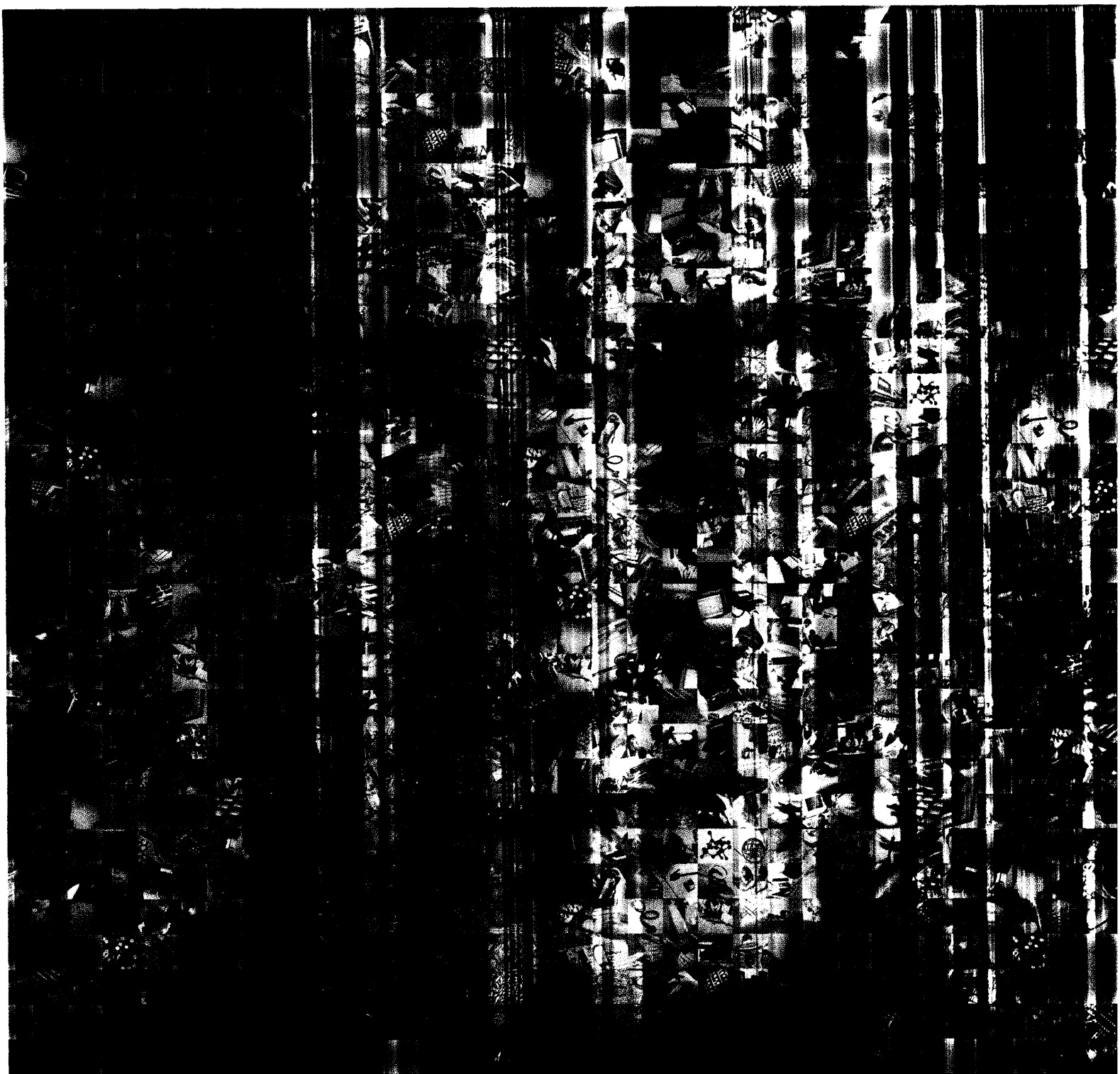

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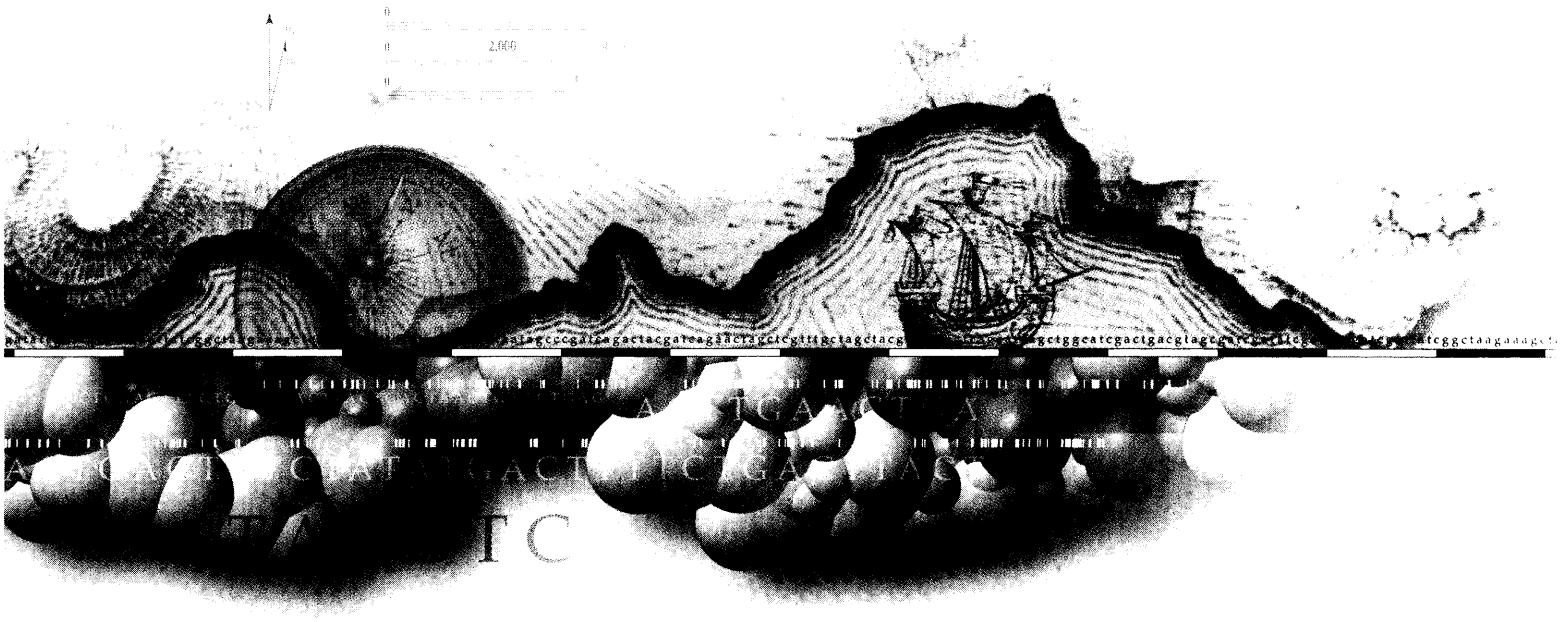

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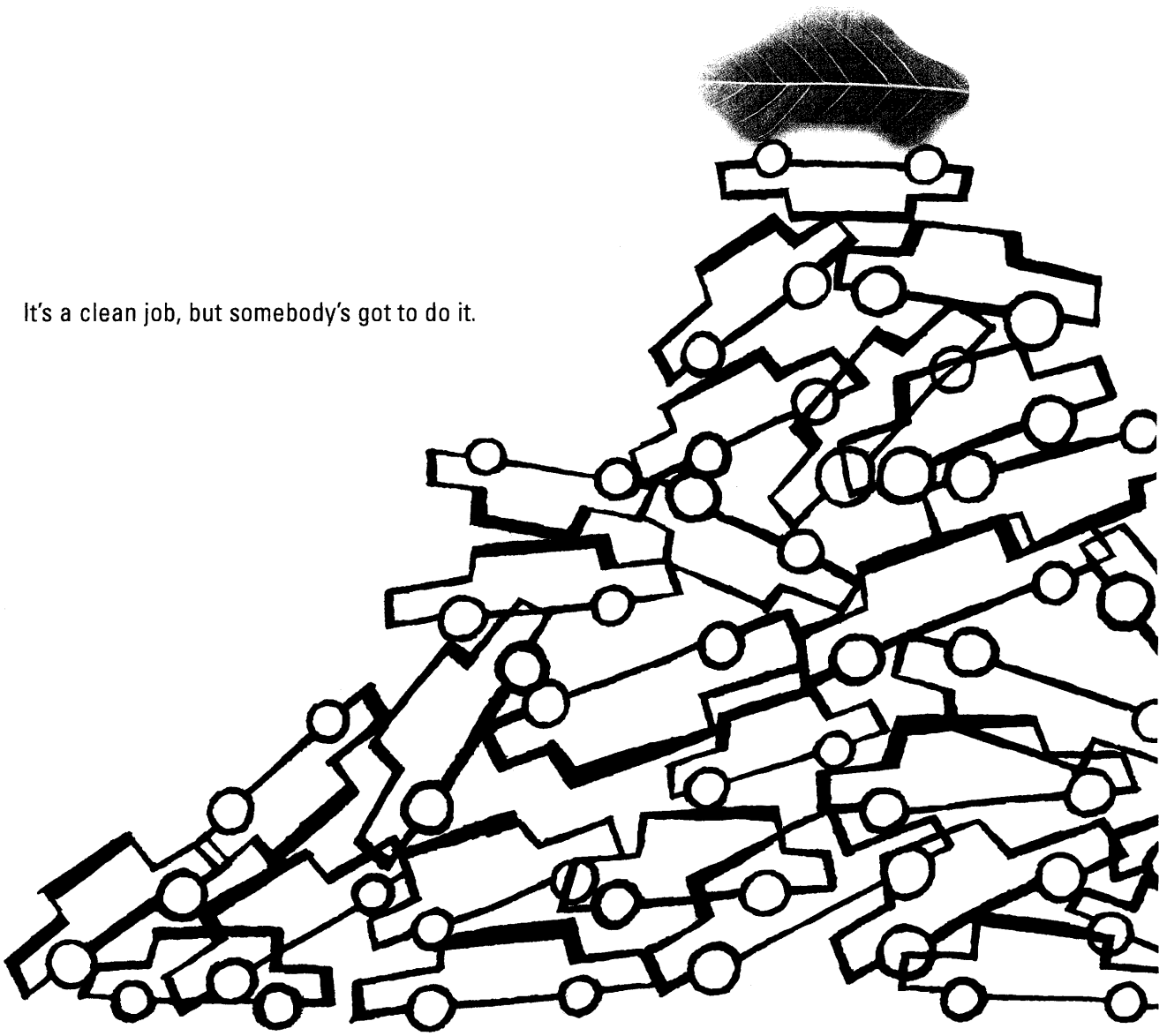

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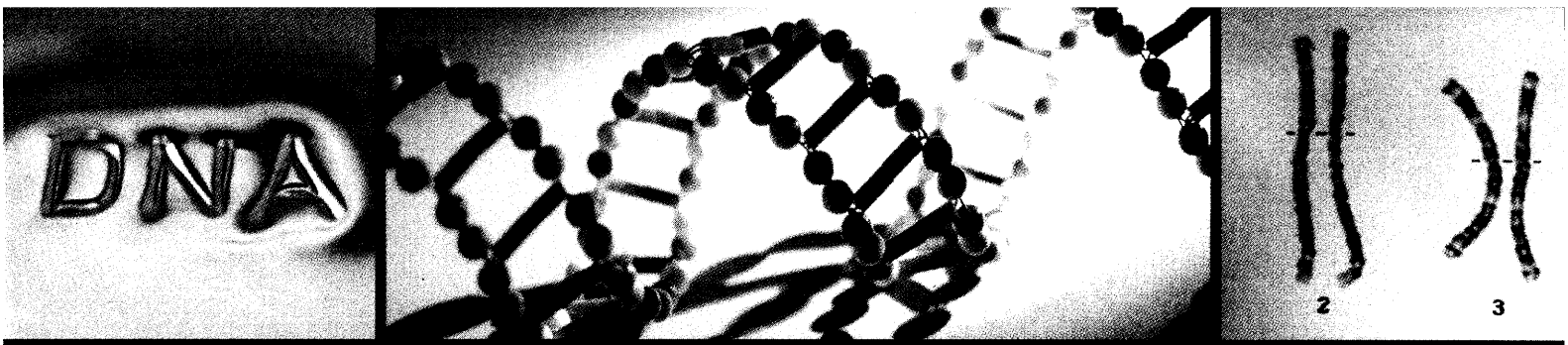

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- Troy Duster, University of California-Berkeley, *Human Genetic Technologies and Taxonomies: Old Wine in New Bottles and New Wine in Old Bottles*
- Donald Kennedy, Stanford University and *Science* Magazine, *New Tests for Science*
- Neal Lane,* Assistant to the President for Science and Technology, *The Grand Challenges of Nanotechnology*

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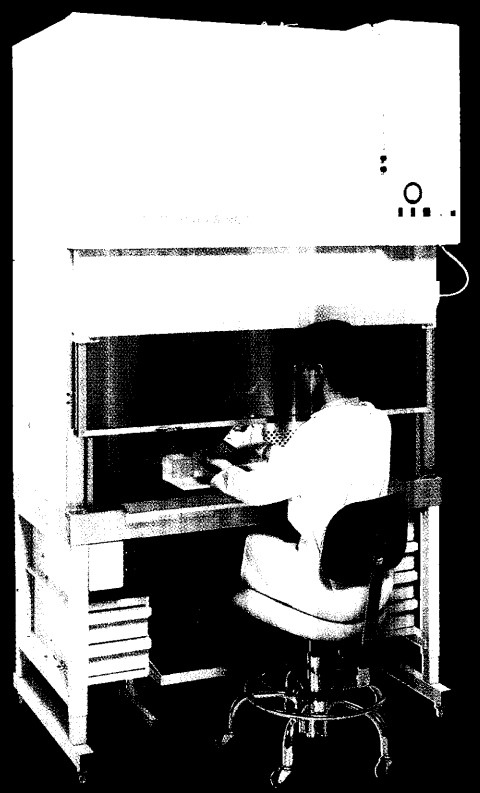

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Special Scientific Events

(Topics with Confirmed Speakers/Organizers as of 12/6/00)

Educational Sessions and Methods Workshops

(Saturday Afternoon, March 24, 2001)
(Chairpersons listed in parentheses)

Biomarkers for Cancer Prevention and Molecular Epidemiology
Tumor Immunology **(Drew M. Pardoll)**
New Therapeutic Targets **(Tona M. Gilmer)**
The Human Genome in Cancer Research **(Paul S. Meltzer)**
Apoptosis in Drug Development and Therapy **(John A. Hickman)**
Approaches in Drug Development and Toxicology **(Michael Morin)**
Signal Transduction: Pathway and Cell Biology **(Michael J. Weber)**
Stem Cell Biology
Tumor Microenvironment
The Future of Molecular Imaging **(Norman C. Coleman)**
Cell Senescence and Cancer **(Bruce Howard)**
Genetics and Cancer Susceptibility
Proteomics **(Lance A. Liotta)**
Gene and Protein Array Technology
Vectors for Gene Delivery

Official Opening Event

(Sunday Morning, March 25, 2001)

Plenary Session **(Stanley J. Korsmeyer)**
Genetics **(Arnold J. Levine)**
Gene Expression Profiling **(Jeffrey M. Trent)**
The Role of Comparative Biology in Understanding Molecular Mechanisms of Cancer **(Elaine A. Ostrander)**
Mouse Genetic Models **(Allan Balmain)**
Genomics to Successful Treatments **(Brian J. Druker)**

Symposia

Protein Degradation, Ubiquitin, and Proteasome **(Alexander J. Varshavsky)**
Animal Models **(Leonard I. Zon)**
Characterization of Molecular Changes in Tumors of Cancer Detection and Prognosis **(David Sidransky)**
Chromosomal Translocations in Hematopoietic Malignancies: From Causation to Therapeutics **(Janet D. Rowley)**
Behavioral Genetics and Cancer **(Neil E. Caporaso)**
Angiogenesis **(Judah Folkman and Robert S. Kerbel)**
DNA Repair Mechanisms **(Steven A. Leadon and Richard D. Wood)**
Stem Cell Biology **(Connie J. Eaves)**
In Vivo Imaging **(Ralph Weissleder)**
Gene Expression and Cell Growth Control **(James L. Manley)**
Chromatin and Nuclear Organization **(Beverly M. Emerson)**
Prevention of Breast Cancer: Molecules to Clinical Trials **(Edison T. Liu)**
Antibody-based Therapeutics **(Susan D. Hellmann)**
DNA Damage Signaling **(Stephen J. Elledge)**
Force, Function, and Form **(Michael P. Sheetz)**
Chemical Genetic Approaches to Ligand Discovery **(Gregory L. Verdine)**
Nervous System Tumors **(Howard A. Fine)**
Wnt Signaling and Cancer **(Hans Clevers)**
Cellular Senescence **(Judith Campisi)**
Tumor Hypoxia **(Amato J. Giaccia)**
How Do We Capitalize on the New Tools of Genomics in Cohort and Case-control Studies of Cancer? **(Nathaniel Rothman and Stephen Chanock)**
Molecular Targeted Cancer Therapeutics **(Lawrence J. Marnett)**
Apoptosis **(Gerard I. Evan)**
New Directions in Prostate Cancer Research **(Cory Abate-Shen)**
Cell Cycle **(Charles J. Sherr)**
New Frontiers in Cancer Research
The Impact of Intracellular Matrix on Tumor Progression **(Lynn M. Matrisian)**
Colon Cancer Up Close: The Molecular View **(Sanford Markowitz)**
Cancer Survivors: Risk of Subsequent Cancers **(Leslie L. Robison)**
Tumor Suppressor Genes as Therapeutic Targets **(Andrei V. Gudkov)**

Forums

Genetic Therapy: Where Do We Go from Here? **(Arthur W. Nienhuis)**
Cancer Screening **(Robert W. Day)**

"Meet-the-Expert" Sunrise Sessions

Pharmacogenomics **(Mary V. Relling)**
Mechanisms of Multidrug Resistance in Cancer Cells **(Michael M. Gottesman)**
Cancer and the Microenvironment **(Mina J. Bissell)**
Genomic Imprinting **(Andrew P. Feinberg)**
Chromosomal Translocations **(Michelle M. LeBeau)**
Bioinformatics **(Andy Baxevanis)**
Treatment of Intraepithelial Neoplasia **(Joyce A. O'Shaughnessy)**
Transcription Factors in Cancer **(James R. Downing)**
Modification of ras Proteins **(Dafna Bar-Sagi)**
Proteomics **(Peter S. Nelson)**
Molecularly Targeting Breast Cancer **(Marc E. Lippman)**
Pharmacogenetics in Mouse Models **(Scott W. Lowe)**
Genomic Instability **(Thea D. Tlsty)**
The p53 Family **(Carol Prives)**
New Aspects of Signaling Cross-talk Between IFNs and Other Cytokines **(Tadatsugu Taniguchi)**
TGFβ Signaling in Tumor Suppression and Progression **(Harold L. Moses)**
Bone Marrow Transplantation
Clinical Prevention Trials **(David S. Alberts)**
Chronic Stimulation of Signal Transduction Pathways: Implications for Cancer Diagnostics and Therapy **(Thomas M. Roberts)**
Proteins Inhibiting the G1 Cyclin-Dependent Kinases that Regulate the Cell Cycle **(Andrew Koff)**
Molecular Determinants of Drug Susceptibility: Genomic Paradigms for Cancer Treatment **(William N. Hait)**
The Many Substrates and Functions of ATM **(Michael B. Kastan)**
IGF1 and Cancer
Pathways in Cytokine Signaling **(James N. Ihle)**
Gene Expression Profiling
Etiology of Adult Leukemias: An Overview and Recent Developments **(Martha Linet)**
Breast Cancer **(Carlos L. Arteaga)**
Telomerase: Diagnostics, Cancer Therapeutics, and Tissue Bioengineering **(Jerry W. Shay)**
The PTEN Tumor Suppressor **(Ramon Parsons)**
Gene-Environment Interactions in Colorectal Neoplasia **(John D. Potter)**
Mechanisms of Carcinogenesis **(Cheryl Lyn Walker)**
Drug Discovery in the p53 Pathway **(David P. Lane)**
Altered DNA Methylation – The Signature for Cancer as a Disorder of Chromatin Organization **(Stephen B. Baylin)**
Myc in the Millenium **(Linda J. Z. Penn)**
Apoptosis
Antisense Strategies **(Alan M. Gewirtz)**

Additional topics to be announced.

Program Updates, Registration & Housing Online *www.aacr.org*