10 August 2001

Science

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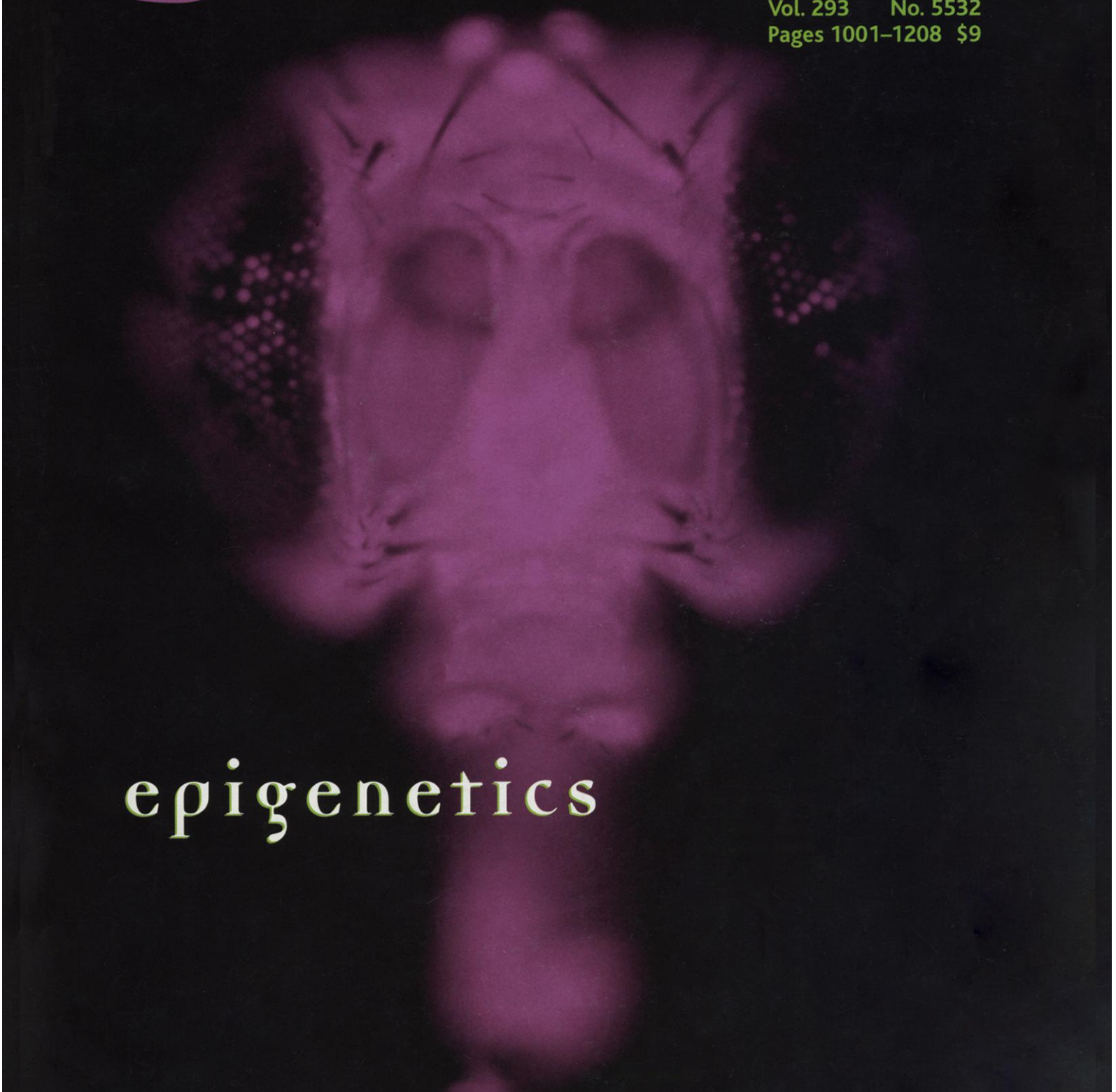
Pages 1001–1208 $9



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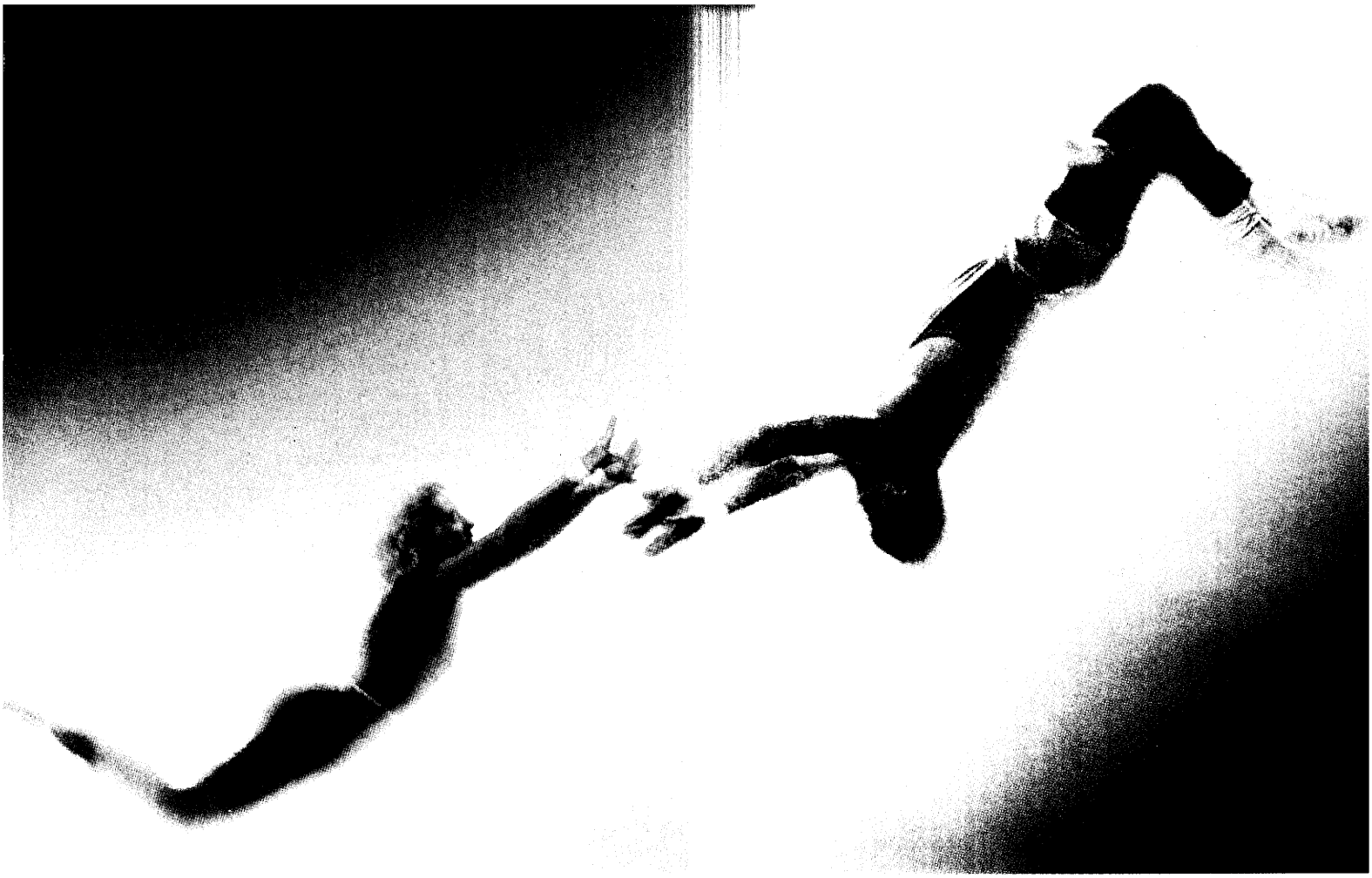

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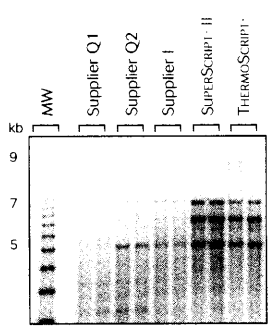

Comparison of yields of cDNA synthesis using various reverse transcriptases.

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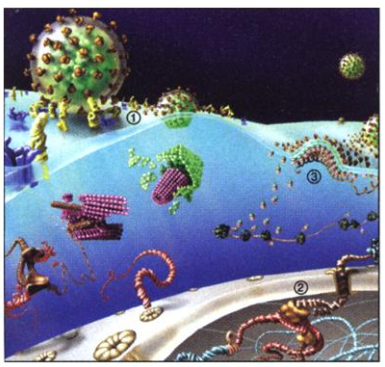
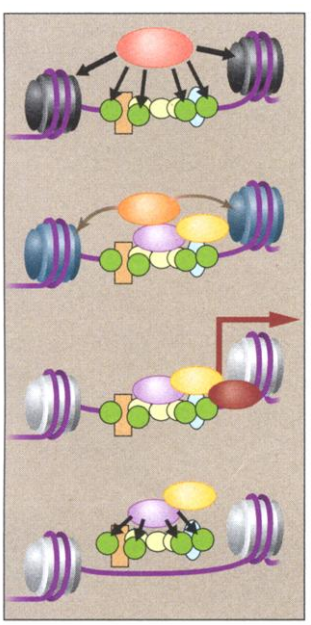


1034
Dismantling HIV

NEWS

1037
Mass extinction witness

SCIENCE'S COMPASS



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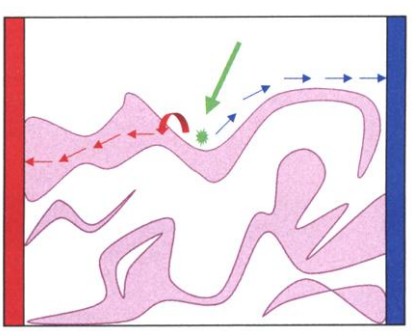
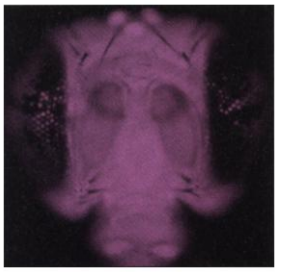
Enhancing gene regulation



1059
Toward organic solar cells

EPIGENETICS

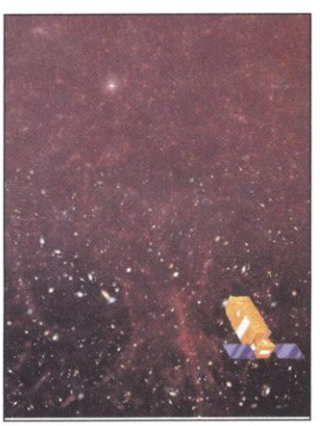
See also Reports on pp. 1142, 1146, and 1150; www.sciencegenomics.org/resources/res_epigenetics.shtml; and Litt* et al. *in* Science *Express (see p. 1007).



COVER 1063

False-color image of the head of a fruit fly, showing the stochastic epigenetic silencing of a transgene encoding green fluorescent protein in individual ommatidia of the eyes. The importance of epigenetics in regulating gene activity is discussed in a special section in this issue. [Photo by Kami Ahmad]

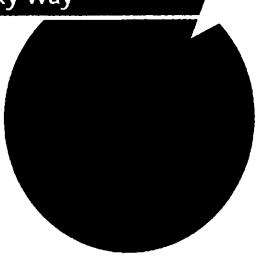
RESEARCH



1112

Seeing the space between

New on *Science* Express Extragalactic x-ray sources in the Milky Way



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Origin of the Hard X-ray Emission from the Galactic Plane
K. Ebisawa, Y. Maeda, H. Kaneda, S. Yamauchi

Deep x-ray imaging suggests that the ridge of plasma along the Galactic plane is from extragalactic sources, possibly supernova remnants.

Correlation Between Histone Lysine Methylation and Developmental Changes at the Chicken β-Globin Locus M. D. Litt, M. Simpson, M. Gaszner, C. D. Allis, G. Felsenfeld

Methylation of H3 lysine 9 correlates with inactive heterochromatic regions, methylation of H3 lysine 4 correlates with active euchromatic regions, and acetyaltion of the histone tail at the boundary may help separate the two chromatin domains.

Loss of Caveolae, Vascular Dysfunction, and Pulmonary Defects in Caveolin-1 Gene-Disrupted Mice M. Drab *et al.*

A caveolin-1 knockout mouse is viable but lacks caveolae and has vascular and pulmonary problems.

TECHNICAL COMMENTS

The Effectiveness of Parks

Bruner *et al.* (Reports, 5 Jan. 2001, p. 125) surveyed 93 protected areas in 22 countries to test whether parks "are an effective means to protect tropical biodiversity." They found that park effectiveness correlated with "basic management activities such as enforcement, boundary demarcation, and direct compensation to local communities"—a result, they suggested, that argues for increased park funding. Vanclay, in a comment, takes issue with the statistical measure used by Bruner *et al.* to gauge effectiveness, presents alternative analyses suggesting that only two variables (boundary demarcation and the involvement of local educators) are relevant to park effectiveness, and argues that Bruner *et al.* presented no evidence to support the conclusion that increased funding will improve park effectiveness. Bruner *et al.* respond that Vanclay's analyses "largely support rather than detract from our findings," present additional details in support of the original study's methodological soundness, and note that Vanclay's analysis, like theirs, suggests that "increased support for management (financial and otherwise) will increase effectiveness."

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/293/5532/1007a

science's stke www.stke.org

Perspective: GABA May Act as a Self-Limiting Trophic Factor at Developing Synapses
A. R. Kriegstein and D. F. Owens

Turning an excitatory synapse into an inhibitory one.

Protocol: RNA Interference of Gene Expression (RNAi) in Cultured *Drosophila* Cells
C. A. Worby, N. Simonson-Leff, J. E. Dixon

Methods for knocking out genes in cells using RNAi.

science's next wave www.nextwave.org

Germany: For Our Children's Children K. Töpfer

The Executive Director of the United Nations Environment Programme highlights the power of science in solving environmental problems, not creating them.

US: Alleviating Tenure Torture C. Trower

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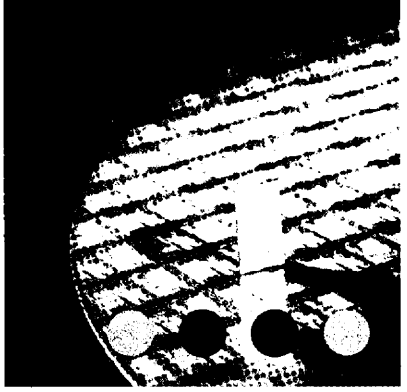

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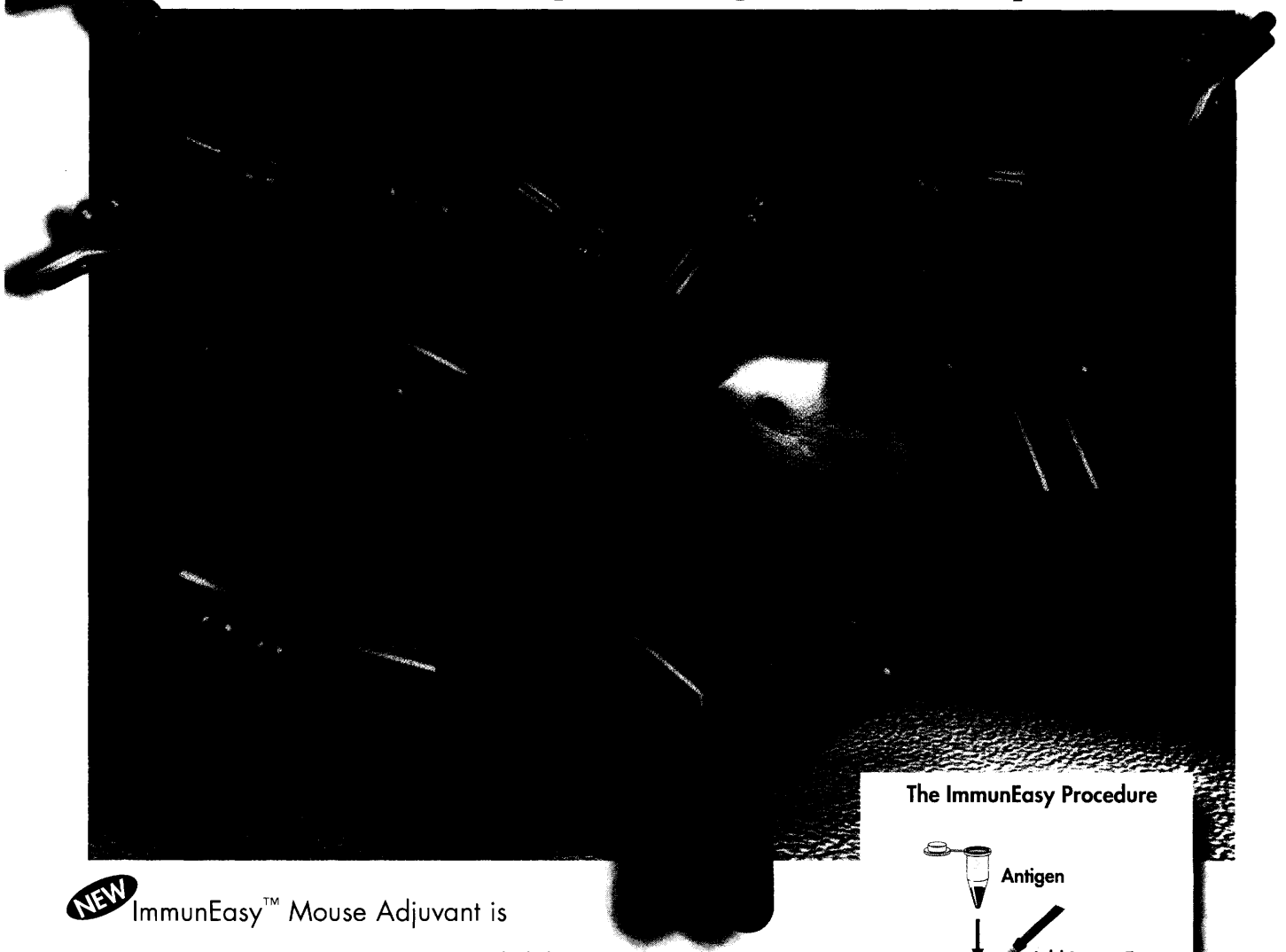

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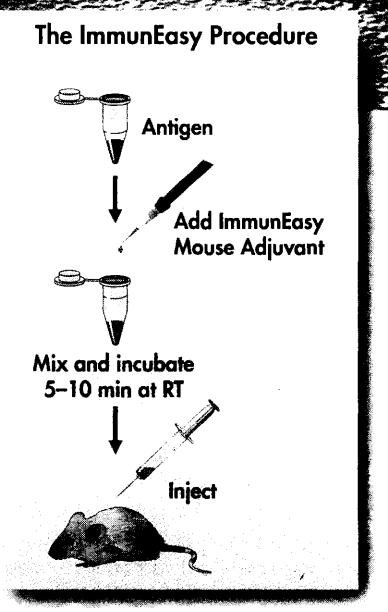

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THIS WEEK IN Science

edited by Phil Szuromi

Perturbed Planet Formation

In the standard model for terrestrial planet formation in our solar system, enhanced accretion of planetesimals occurred in a protoplanetary disk to form much larger planetesimals that eventually formed planets. Kortenkamp *et al.* (p. 1127) show that this process could be efficient if drag from solar nebular gas and perturbations from a larger companion (such as a giant planet, a brown dwarf, or another star) were included. This different mode of "runaway growth" might be useful to explain the formation of extrasolar planetary systems and to estimate whether terrestrial-like planets may exist deep within opaque accretionary disks.

1119 Solar Cell Organization

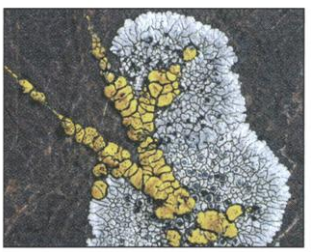
In organic solar cells, absorbed photons create charge carriers (electrons and "holes") that are taken up by n- and p-type materials that send them to the electrodes. The efficiency of the cell will depend on how closely the n- and p-type materials can be brought into contact. Schmidt-Mende *et al.* (p. 1119; see the Perspective by Nelson) have developed a simple solution-based process in which self-organization creates a nanoscale interface in the organic layer. The hole-accepting material is incorporated as a discotic liquid crystal, which creates columnar structures within the film that are surrounded by an electron-accepting organic dye. This structure leads to efficient charge separation of carriers between the discotic material and the dye.

Structure of the Intergalactic Medium

The intergalactic medium is the gaseous material between luminous structures such as galaxies and clusters. Kriss *et al.* (p. 1112; see the Perspective by Miralda-Escudé) have probed the ionized structure of this gas at intermediate epochs of the universe using the Far Ultraviolet Spectroscopic Explorer (FUSE). Many of the early structures that formed were quasars, and some structures were starburst galaxies. These structures could be found even in low-density regions, which is consistent with the current model of structure formation by gravitational instability.

Precocious Land Plants

The colonization of land by plants, typically put at about 400 million years ago, allowed the establishment of terrestrial ecosystems and the evolution of life on land. Heckman *et al.* (p. 1129; see the news story by Pennisi) pooled molecular data on nuclear protein coding genes drawn from across the spectrum of diversity of living organisms in an attempt to estimate the time of origin of land plants and fungi. The results indicate a substantially earlier origin—perhaps 700 million years ago—for land plants and fungi than is commonly held.



CREDIT: HECKMAN *ET AL.*

Missing a Supermassive Black Hole in M33

Recent work has shown a correlation between the mass of a supermassive black hole at the center of a spiral galaxy and the velocity dispersion in the bulge of the galaxy. Merritt *et al.* (p. 1116; see the 20 July news story by Seife) analyzed spectra from the Space Telescope Imaging Spectrograph (STIS) for the spiral galaxy M33, a member of the Local Group that has almost no central bulge. They estimated an upper limit to the mass of any candidate central black hole to be 3000 solar masses, which is orders of magnitude too low for a supermassive black hole. Thus, either the mass-to-dispersion relation changes for intermediate-mass black holes or these less-massive black holes form by a different mechanism.

Getting Polarization by Design

The integration of photonic band gap (PBG) structures with active lasing media could lead to the development of lasers with superior features such as single-mode emission over large areas, high power, surface emission with a very narrow divergence angle, and controlled polarization. Noda *et al.* (p. 1123) now present a combined theoretical and experimental study that suggests that such devices may not be so far away. The optical properties were computed for a two-dimensional PBG crystal with a square lattice array of holes, and the device was then fabricated. The polarization mode of the emitted light can be controlled in structures with elliptically shaped holes.

Making Proteins in the Nucleus

Translation, in which the ribosome decodes messenger RNA into protein, has been thought to occur exclusively in the cytoplasm of eukaryotic cells and not in the nucleus. However, some aberrant RNAs containing premature termination codons are recognized and degraded in the nucleus, a phenomenon most easily explained if ribosomes are scanning messages in the nuclear compartment. Iborra *et al.* (p. 1139; see the Perspective by Hentze), using three different protein-labeling methods, show that up to ~15% of cellular translation actually occurs in the nucleus. Transcription of the RNA is coupled to translation, as has been found in prokaryotes. One function of these nuclear ribosomes may be to "proofread" newly synthesized RNA transcripts for errors.

A Tale of Histone's Tails

The DNA of all eukaryotes is packaged into chromatin, which is composed largely of histone proteins. Covalent modifications of the tails of these proteins play an important role in both in chromosome organization and in the specific regulation of individual genes. Litt *et al.* (*Science* Express, 9 August) and Noma *et al.* (p. 1150) show that methylation of Lys^4 in the amino-terminal tail of histone H3 is specific to euchromatic domains (where genes are generally active) and methylation of H3 Lys^9 is specific to heterochromatic domains of chromatin (where genes are generally inactive). Inverted repeats flanking the heterochromatin act as boundary elements and preventing its spread into

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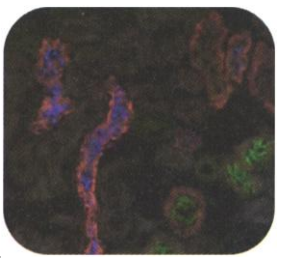
CONTINUED ON PAGE 1011

the surrounding euchromatic regions. At the level of individual genes, Lo *et al.* (p. 1142) show that phosphorylation of Ser^{10} on histone H3 by Snf1 kinase facilitates acetylation of Lys^{14} by Gcn5 (but not vice versa), and that both are needed for the activation of the *INO1* gene in vivo.

Cardiovascular Health Gone in a *WNK*



High blood pressure (hypertension) is one of the principal causes of heart attack, stroke, congestive heart failure, and kidney failure. Wilson *et al.* (p. 1107; see the news story by Marx) identify two related genes that are responsible for a rare form of hypertension called pseudohypoaldosteronism type II, an autosomal dominant trait characterized by abnormalities in renal electrolyte handling. The two genes, *hWNK1* and *hWNK4*, are expressed in the kidney and encode members of a recently described family of serine-threonine kinases. The disease-causing alterations in the *WNK* genes are likely to be gain-of-function mutations that would enhance the expression or activity of the kinases. Because *hWNK4* lies at a locus on chromosome 17 that has been linked to bloodpressure variation in the general population, this gene may also play a role in the most common forms of hypertension.

Pointing the Finger

One difficulty in developing a vaccine against human immunodeficiency virus–type 1 (HIV-1) is that only three isolated human antibodies are potent enough to neutralize this virus in vitro and in vivo. Saphire *et al.* (p. 1155) offer the crystal structure of one of these antibodies, b12, as a clue that may point vaccine developers in a productive direction. Docking this structure onto that of gp120, the envelope protein of HIV-1, suggests that a precisely angled Trp residue inserts into a narrow crevice of gp120 in a fashion that resembles that of a critical Phe residue of CD4, an HIV-1 receptor.

Acetylation Flips the Transcription Switch

Cells respond to external challenges such as viral infection by adjusting gene expression. Viral infection activates the expression of interferon-β (INF-β) via a protein complex, termed the enhanceosome, that forms on the gene's promoter. The interferon enhanceosome recruits two acetyltransferases, PCAF and CBP, that not only acetylate the histone components of nucleosomes but also acetylate the enhanceosome itself. Munshi *et al.* (p. 1133; see the Perspective by Struhl) report that PCAF acetylation of the enhanceosome protein HMG-I at the Lys^{71} residue stabilizes the enhanceosome and protects it from CBP acetylation. However, acetylation of HMG-I by CBP at Lys^{65} leads to the dissociation of the enhanceosome from the DNA molecule. Therefore, the enhanceosome is a dynamic complex that is acted upon by competing acetylations to create a switch that turns transcription on or off.

Coincidence Detection in Pyramidal Neurons

It is not known whether the timing of an action potential in pyramidal cells reports the timing of the afferent activity that triggered the spike. Pouille and Scanziani (p. 1159) compared the temporal precision with which firing is induced in hippocampal neurons by afferent stimuli when synaptic inhibition was functional and when it was suppressed. Inhibition limited the temporal variability of pyramidal cell discharge, and this effect of synaptic inhibition is stronger near the soma than at dendritic sites.

Unraveling the Placebo Effect

The placebo effect has long intrigued medical and pharmacological researchers. De la Fuente-Fernández *et al.* (p. 1164) examined the neural basis of the placebo effect and its role in the treatment of Parkinson's disease (PD) using [^{11}C]raclopride binding as measured by positron emission tomography. The placebo effect in PD is mediated by the specific improvement in dopaminergic neurotransmission through an increase in the release and the synaptic levels of dopamine in the striatum. Although patients receiving an active drug in a placebo-controlled study benefited from the placebo effect, this effect did not synergistically augment the effect of the active drug.

CREDIT: WILSON *ET. AL*

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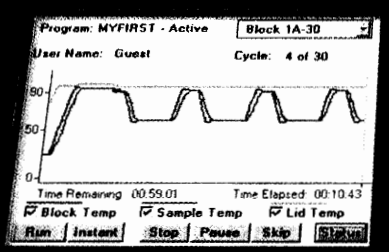

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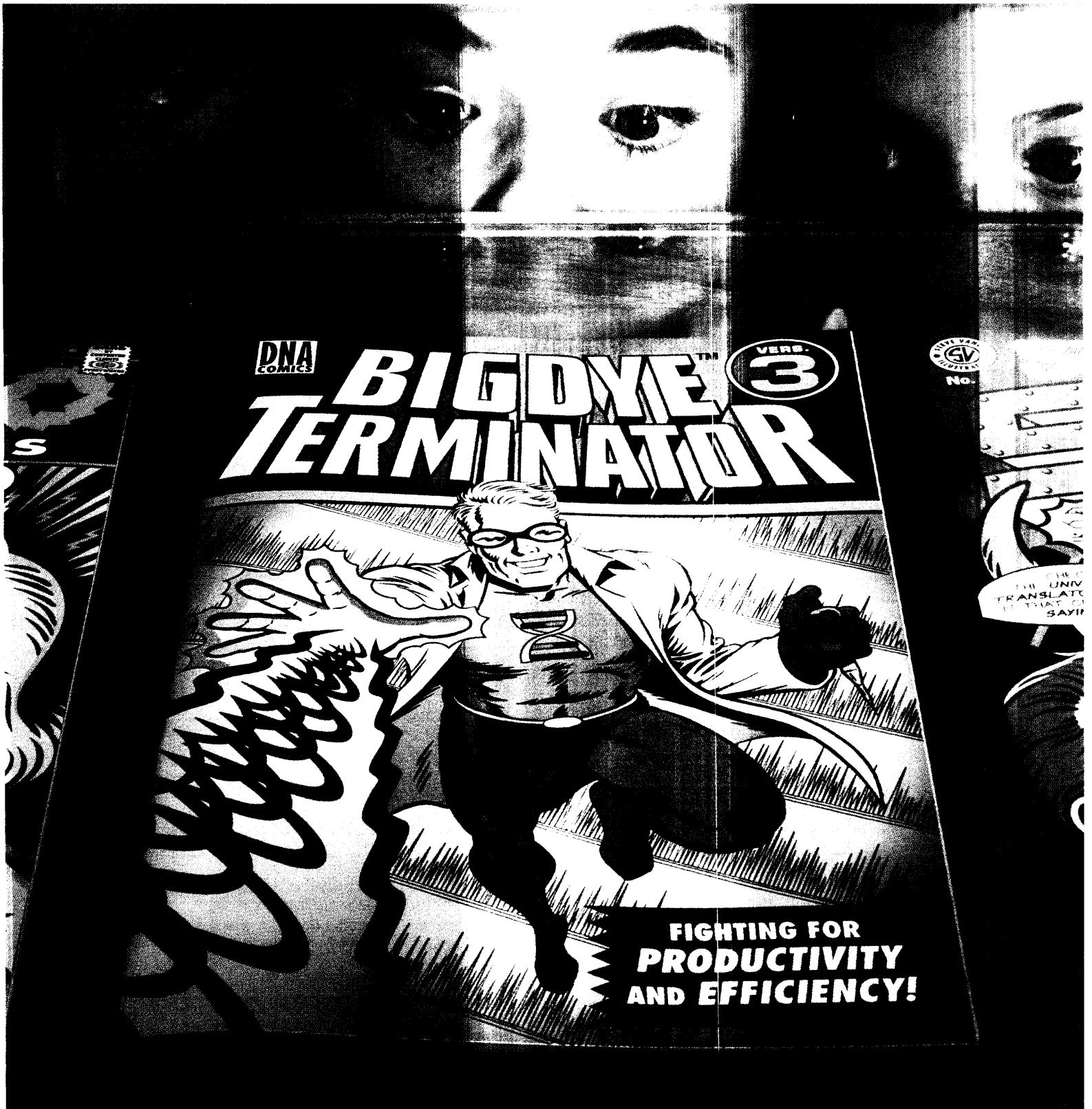

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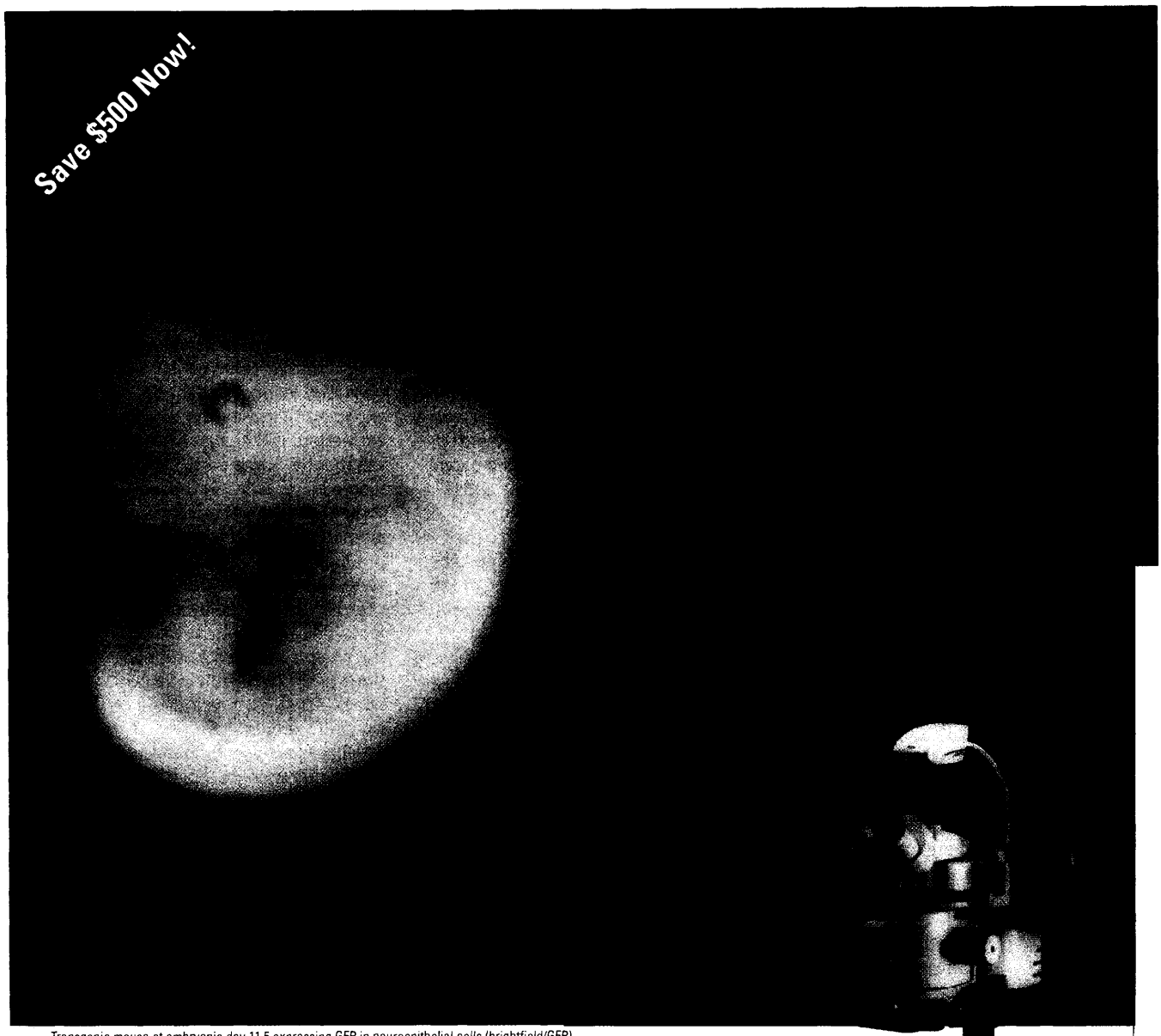

Transgenic mouse at embryonic day 11.5 expressing GFP in neuroepithelial cells (brightfield/GFP)
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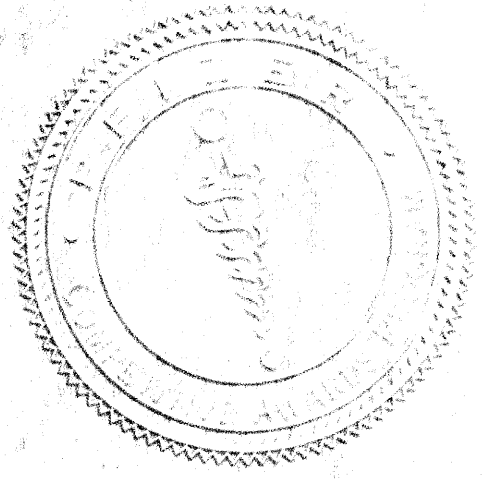

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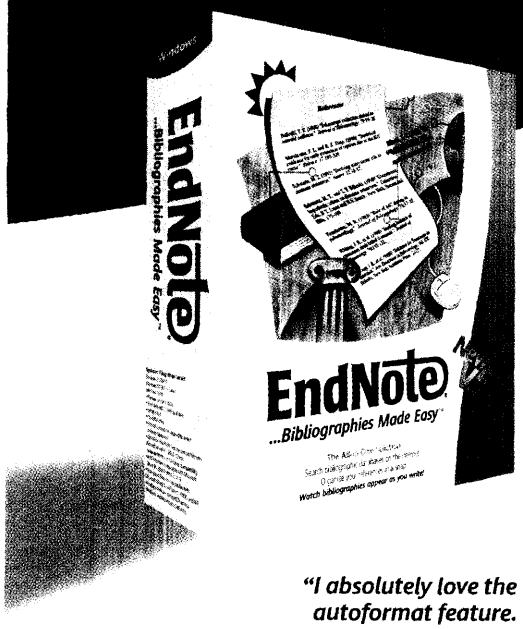

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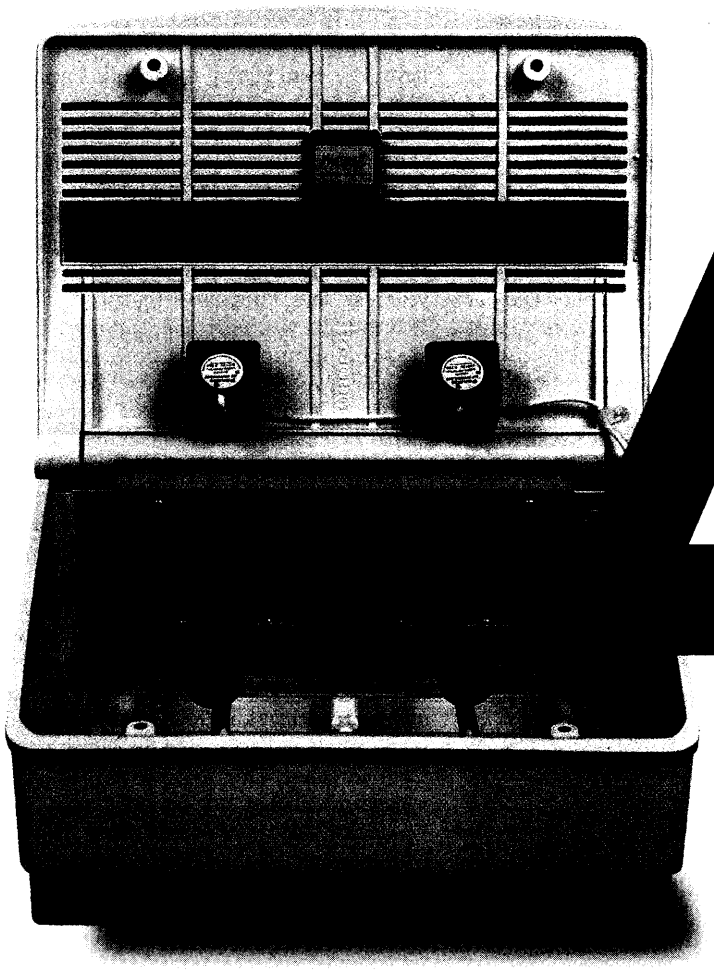

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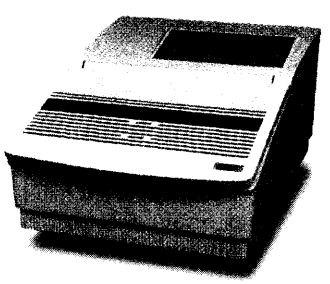

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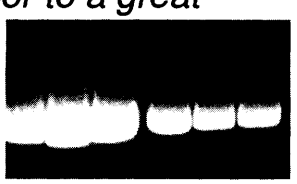

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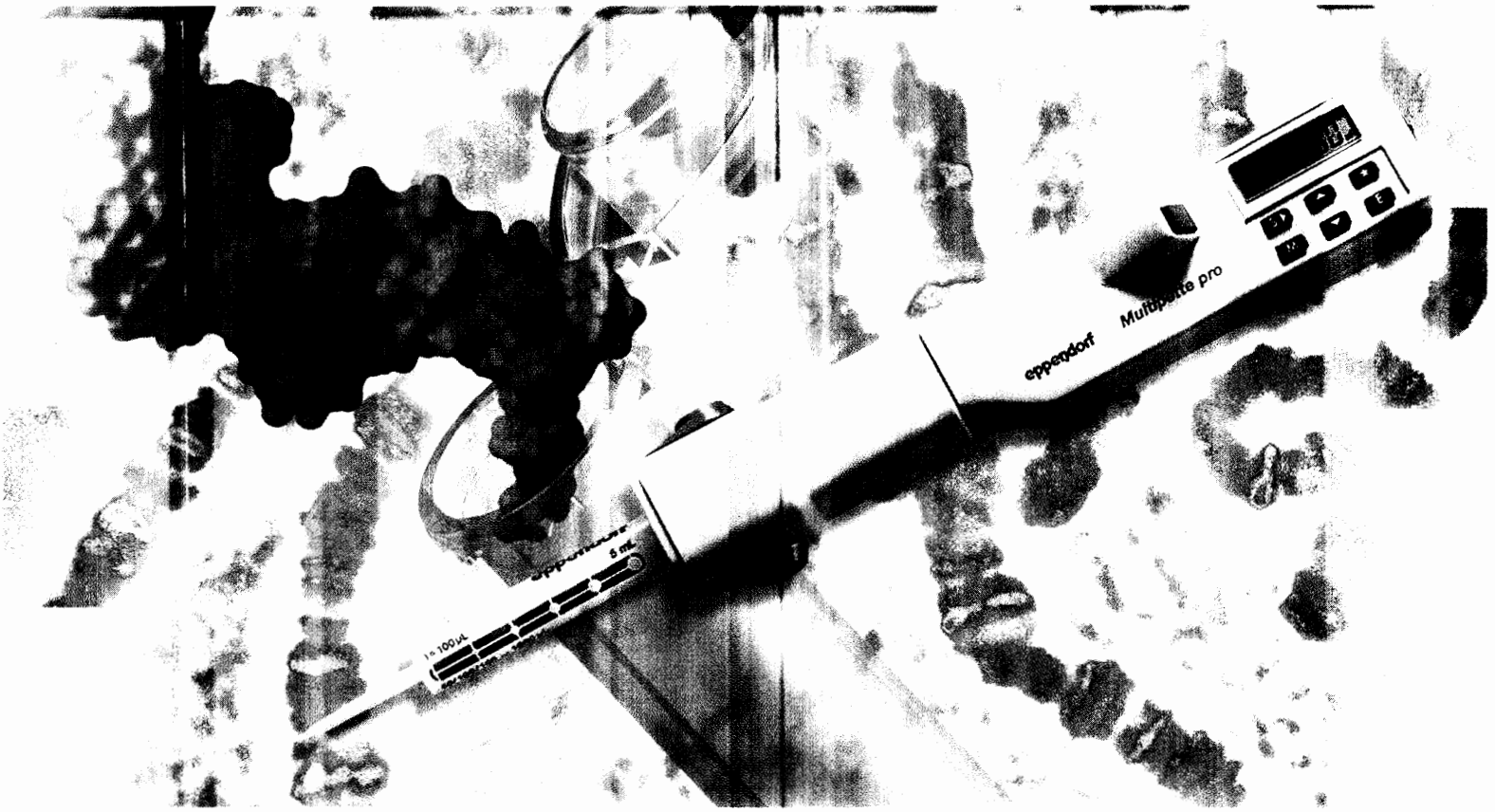

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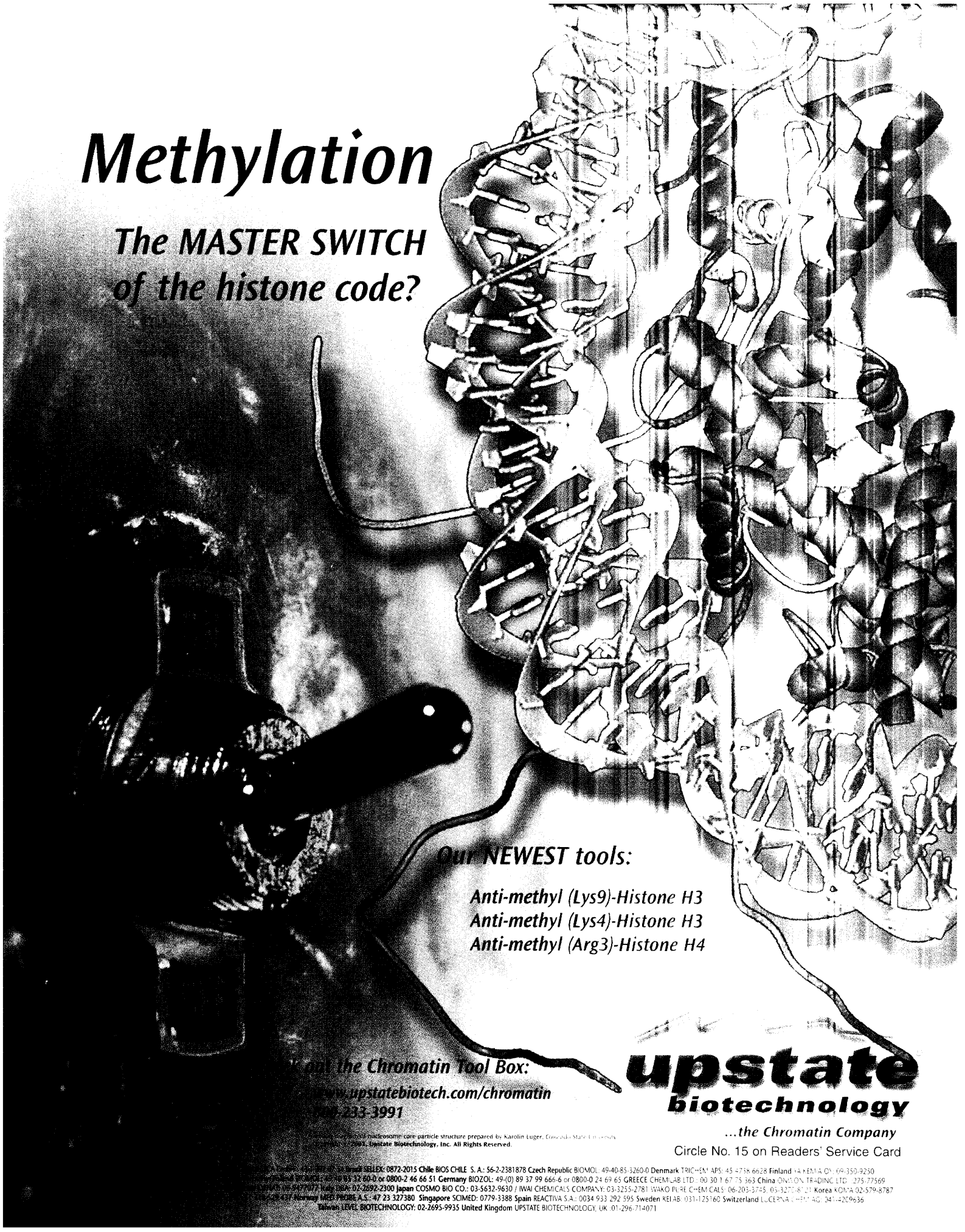

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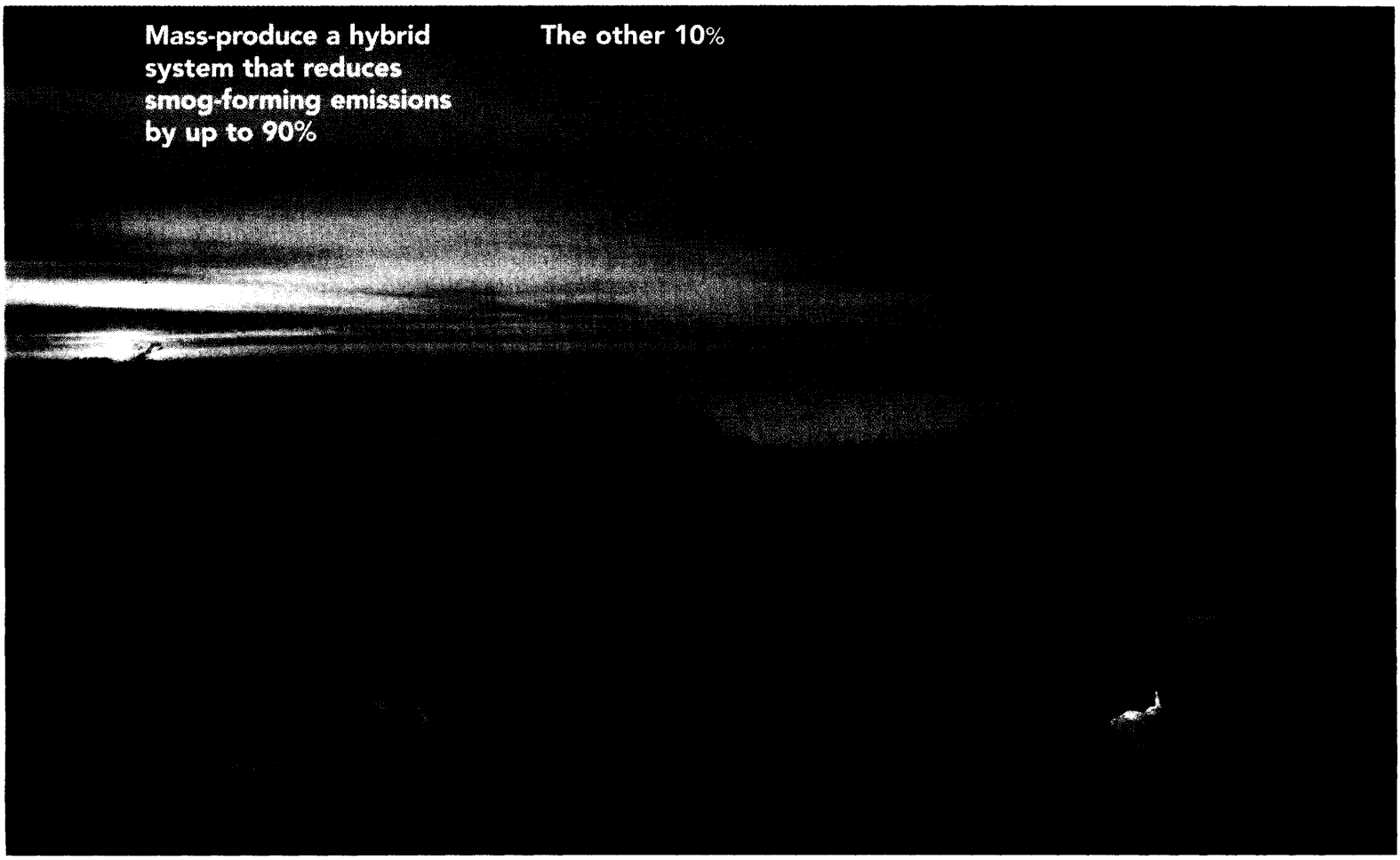

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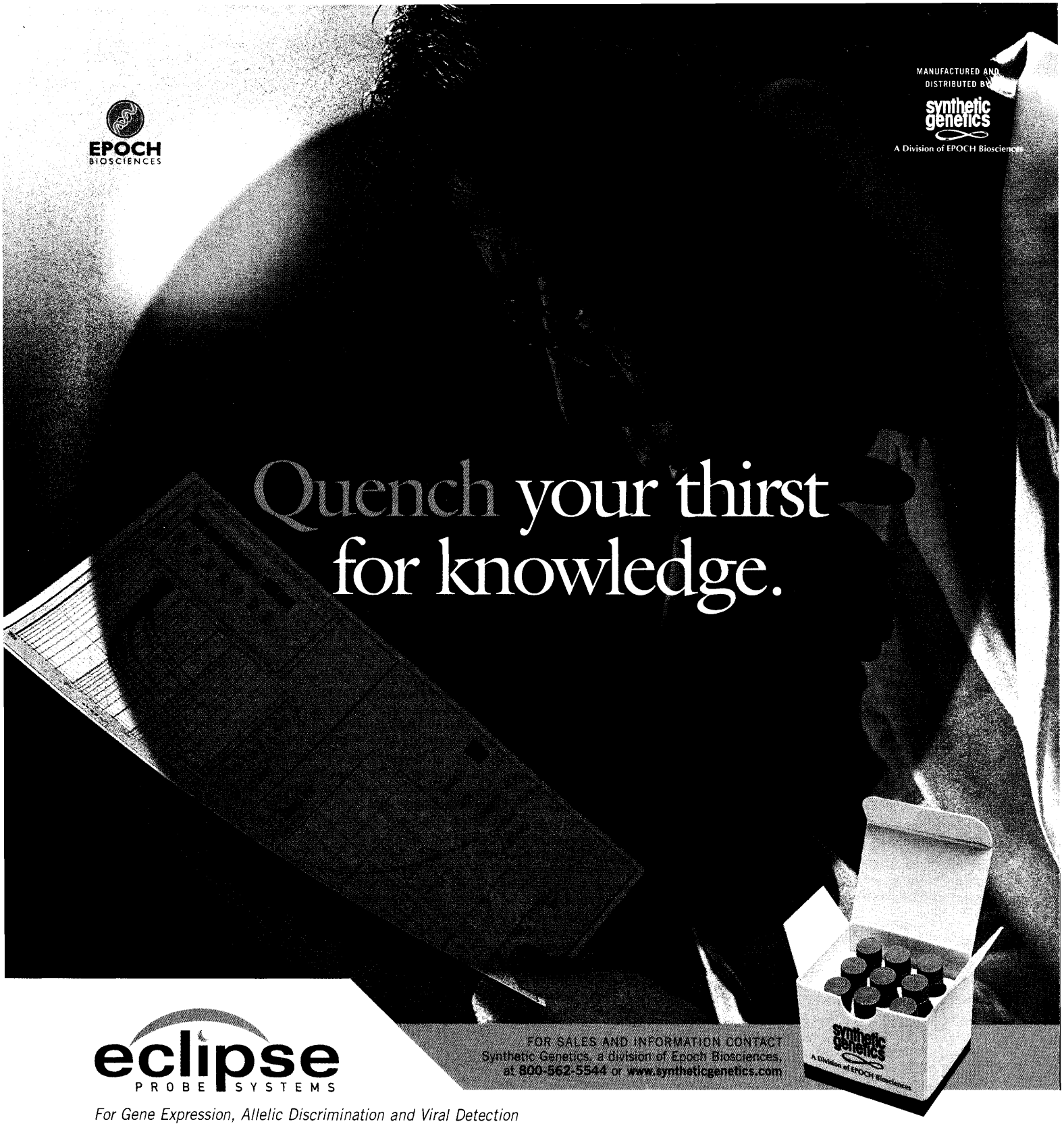

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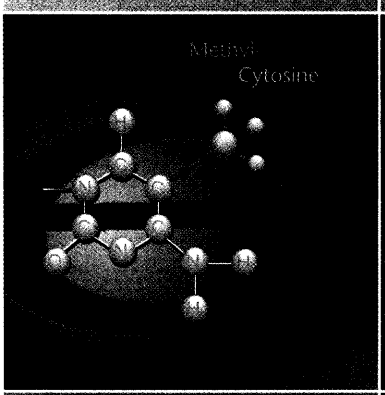
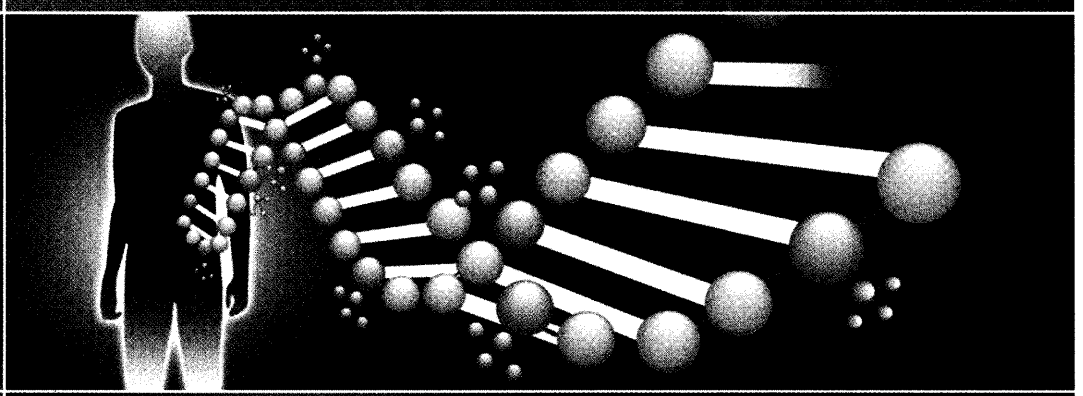
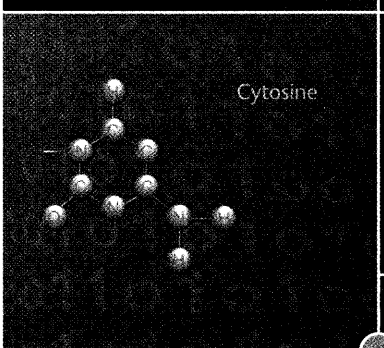
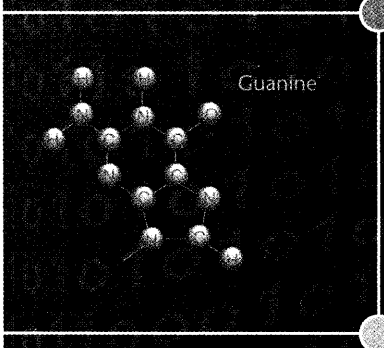
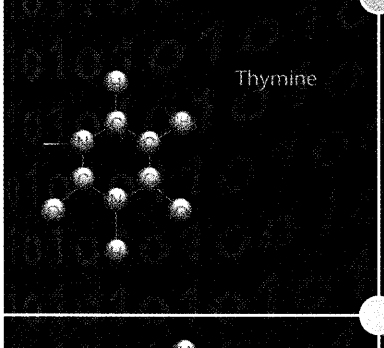


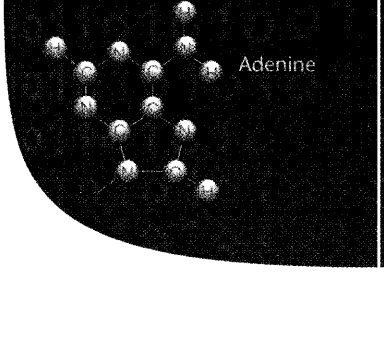




DNA-methylation based solutions for tomorrow´s personalized medicines







Epigenomics offers a totally new approach to fighting disease, covering the entire value chains of Diagnostics and Pharmaceutical Enabling Technologies.

>> Epigenomics´ Diagnostic products:

- Tissue based differential diagnostics for cancer and other proliferative diseases
- Serum or body fluid based diagnostic tests for cancer and other proliferative diseases

>> Epigenomics´ Pharmaceutical Enabling products:

- Assay systems for focused drug discovery and candidate screening
- Target finding and validation
- P atient population grouping and clinical trial design

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