3 August 2001

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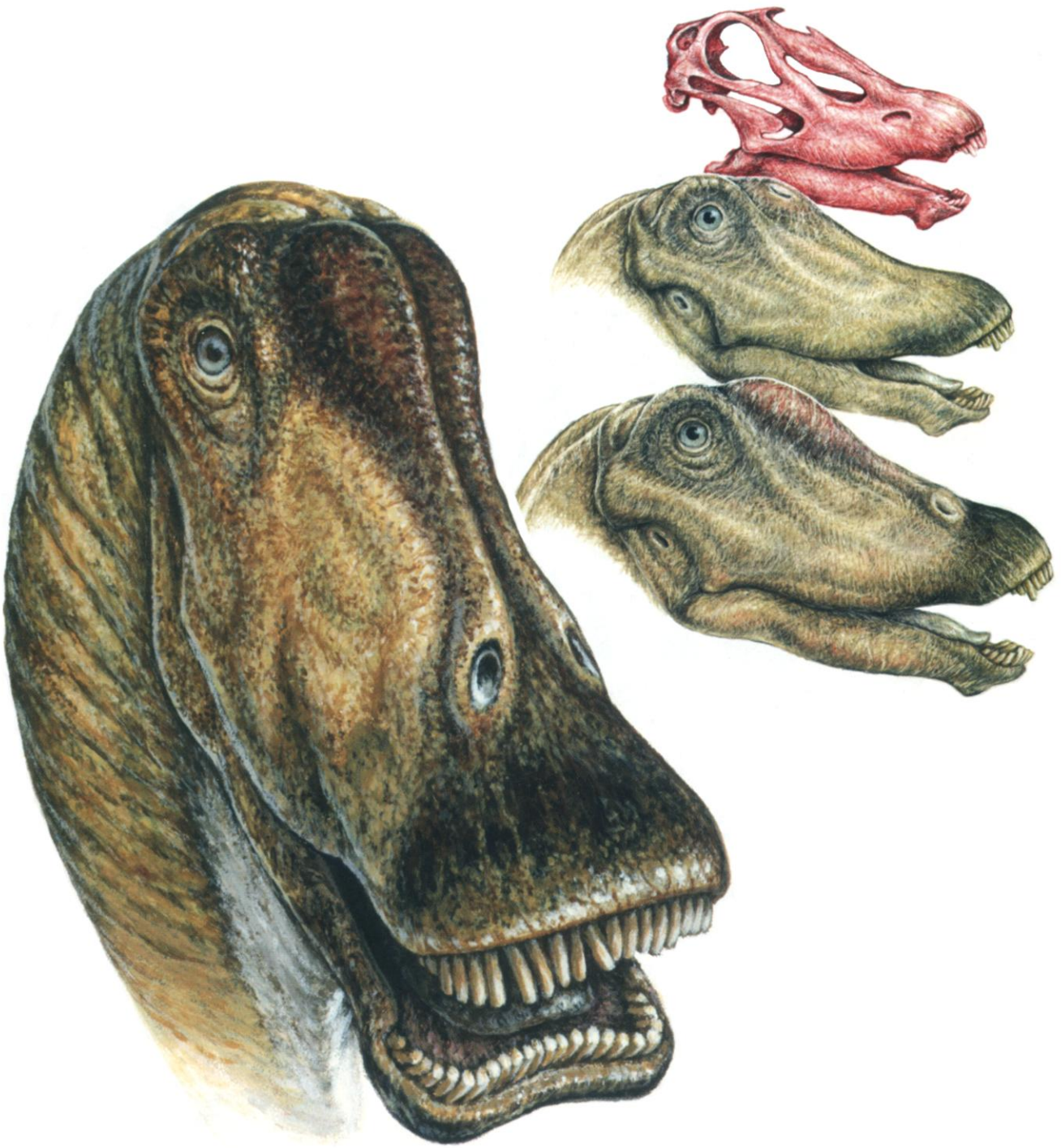
Pages 749–1000 $9



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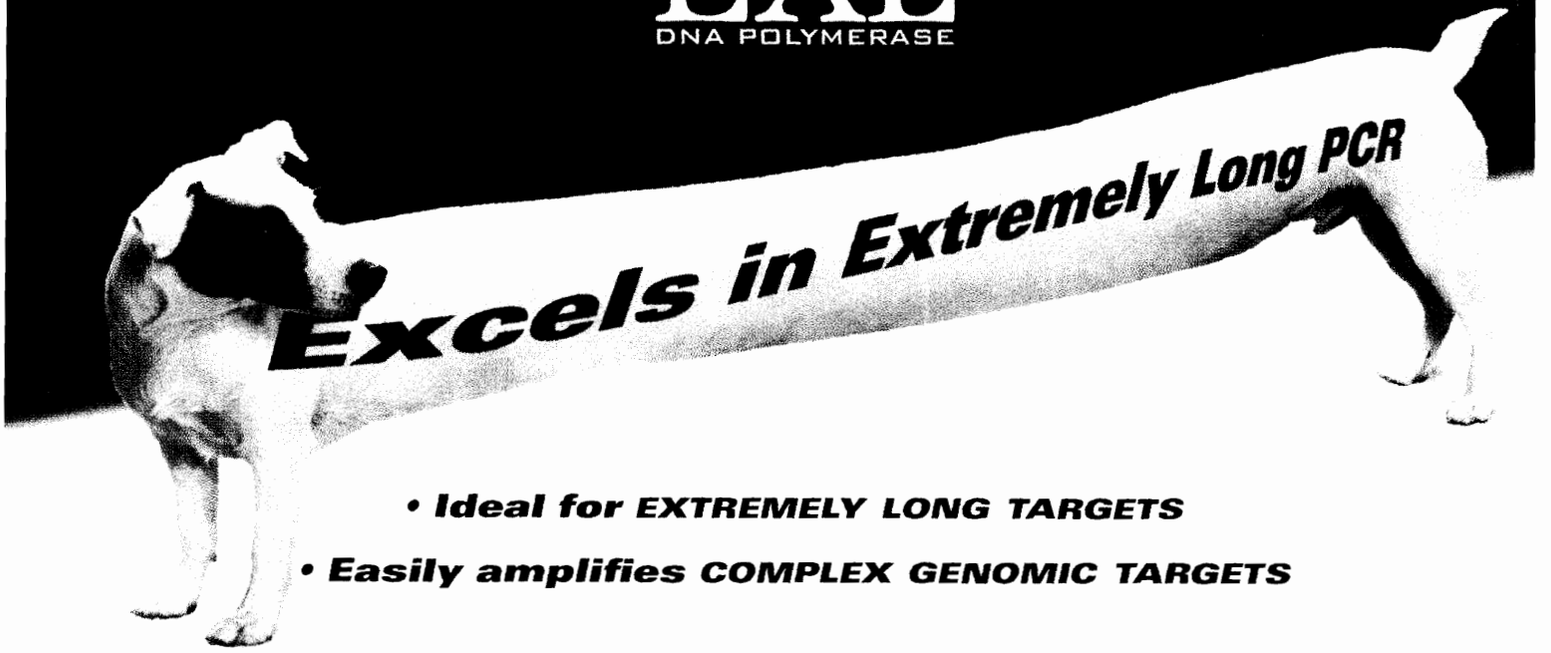

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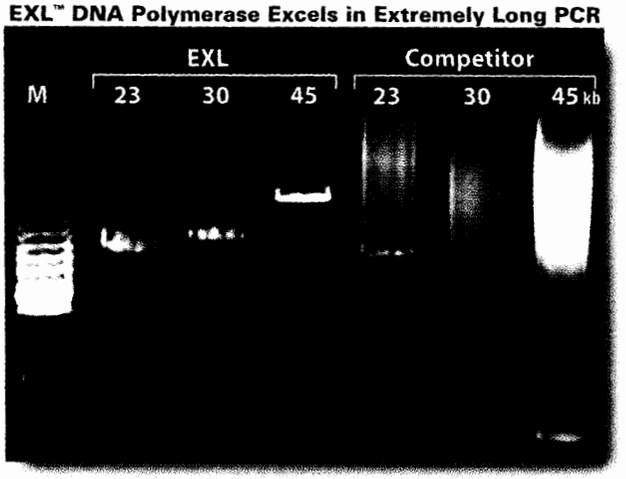

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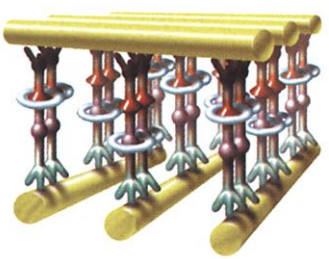
Monitoring Etna's pyrotechnics

NEWS

NEWS OF THE WEEK



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The incredible shrinking circuit

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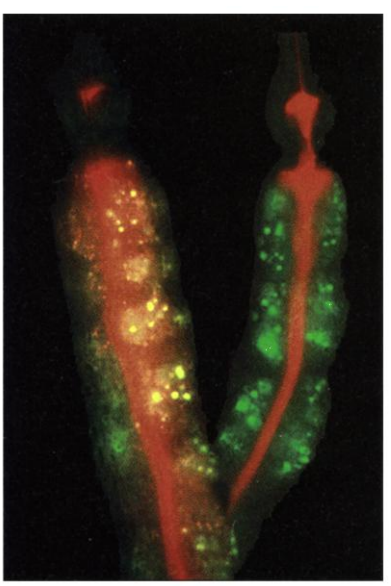
COVER 850

New restoration of the head of the sauropod dinosaur *Diplodocus* (left and bottom right), based on a study reflecting the forward position of the nostrils. Top right is the skull; middle right is the traditional view, refuted by the new research. [Paintings by M. W. Skrepnick under the direction of L. M. Witmer]



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Exploring Bt toxin resistance

New on *Science* Express Microarrays for mesoderm

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Patterns of Gene Expression During *Drosophila* Mesoderm Development E. E. M. Furlong, E. C. Andersen, B. Null, K. P. White, M. P. Scott

DNA microarrays of fluorescent *Drosophila* yield insight into mesoderm development.

A Role for the RNase III Enzyme DCR-1 in RNA Interference and Germ Line Development in *C. elegans* S. W. Knight and B. L. Bass

The enzyme Dicer, thought to be a key component of RNA interference, appears to be important for some, but not all, RNAi effects and also for normal development of the nematode *C. elegans*.

Skinny Hedgehog, an Acyltransferase Required for Palmitoylation and Activity of the Hedgehog Signal Z. Chamoun *et al.*

To function properly during development, the important signaling protein Hedgehog must be palmitoylated at its amino-terminus, a modification apparently catalyzed by an acyltransferase encoded by the *skinny hedgehog* gene.

TECHNICAL COMMENTS

Memory Consolidation and NMDA Receptors

Reporting on experiments that used a third-generation selective knockout technique, Shimizu *et al.* (Reports, 10 November 2000, p. 1170) argued that memory consolidation in mice depends on reactivation of *N*-methyl-D-aspartate (NMDA) receptors in the hippocampal CA1 region after initial learning. Day and Morris, in a comment, find "several reasons to be cautious" about the study's claims, and summarize results of pharmacological experiments in rats that found no effect of "NMDA receptor blockade on memory consolidation." Those results, in their view, suggest that memory consolidation hinges on "posttraining neural activity in the hippocampus, but not synaptic plasticity," as suggested by the synaptic reentry reinforcement (SRR) model of Shimizu *et al.* In a response, Shimizu *et al.* assert that several "important technical issues lead us to question the accuracy" of the results cited in the comment, and that Day and Morris "may have misunderstood some aspects of our SRR model."

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/293/5531/755a

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Perspective: Neuronal Signaling through Alternative Splicing—Some Exons CaRRE . . . K. J. O'Donovan and R. B. Darnell

Alternative splicing mediated by calcium calmodulin kinase alters neuronal channel composition.

Perspective: New Roles for Introns—Sites of Combinatorial Regulation of Ca^{2+}- and Cyclic AMP–Dependent Gene Transcription S. Finkbeiner

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Global: Saving the Planet

Our August feature explores careers in the environmental sciences—where opportunities encompass not only research in climate change, bioremediation, and biodiversity, but also careers in environmental advocacy, lobbying, and writing and editing.

Canada: No Secrets—Preparing for a Startup Interview R. Wintle

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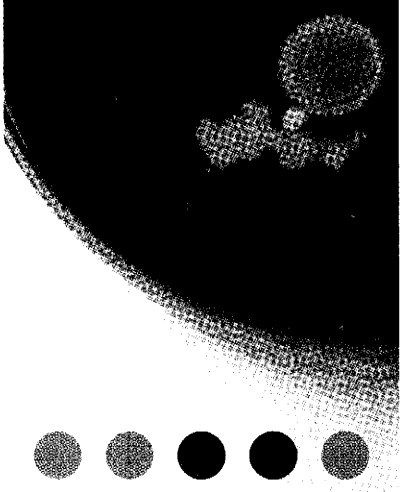

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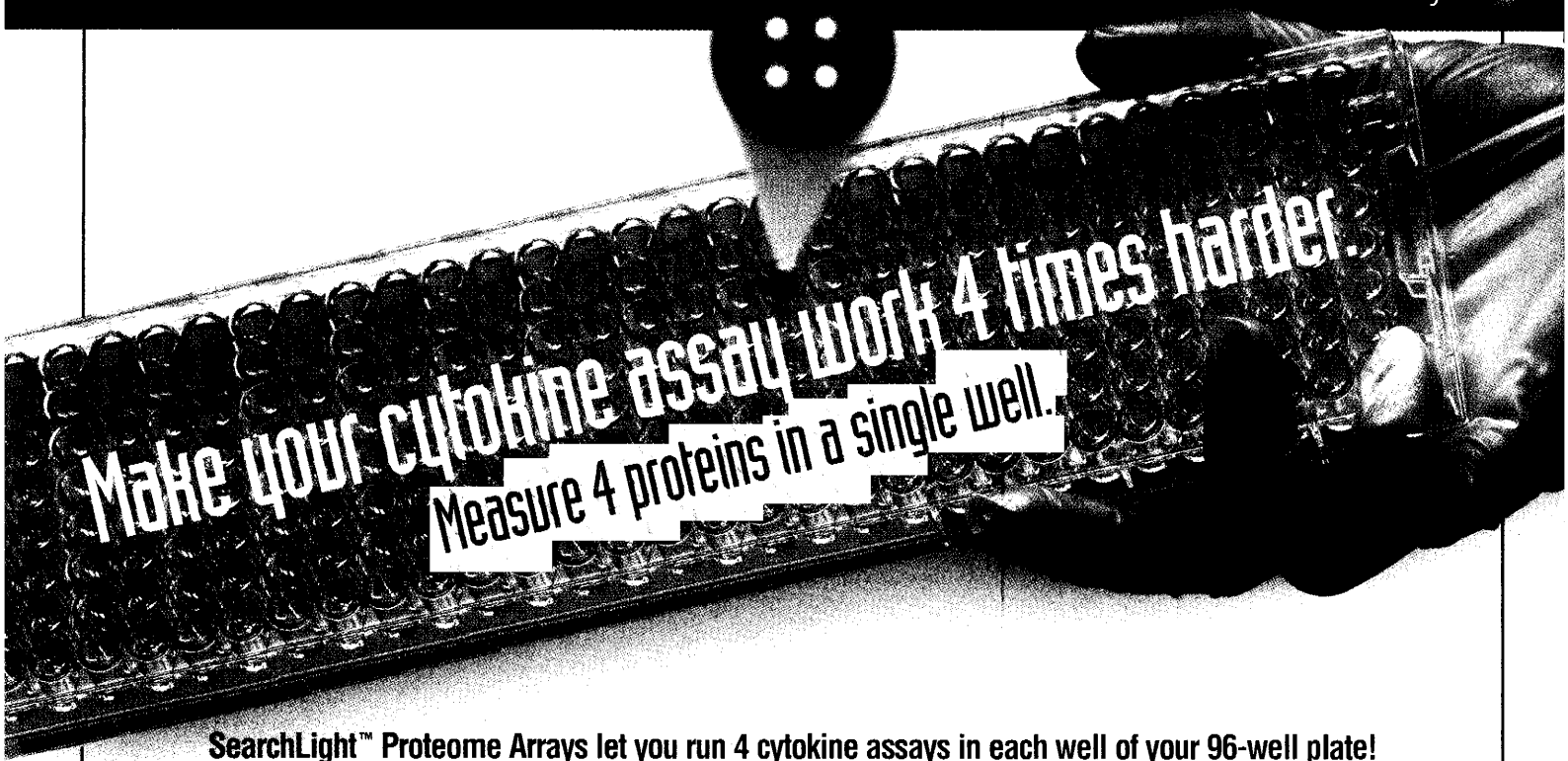

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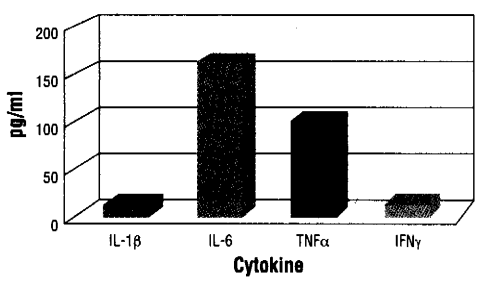

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THIS WEEK IN Science

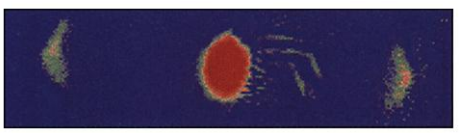
edited by Phil Szuromi

Oxidizing Earth

The Earth's early environment was relatively poor in oxygen, and observations and modeling indicate that the rise in oxygen levels did not occur until long after oxygen-enriching bacterial photosynthesis had developed. Catling *et al.* (p. 839; see the Perspective by Kasting) explain the apparent disconnect between oxygenation and the start of photosynthesis by adding methanogenesis to the process. Photosynthesis split water into O_2 and H_2, and then methanogenesis used H_2 to generate CH_4. Finally, ultraviolet photolysis converted CH_4 and O_2 into CO_2, O_2, and H_2. The escape of H_2 into space allowed the buildup of O_2.

843 Atomic Josephson Junctions

When two boson condensates are separated by a thin barrier, their phases can couple through wave function overlap and give rise to periodic tunneling. This Josephson Effect, long known in superconductors and more recently in superfluids, has now been demonstrated in a readily tunable Bose-Einstein condensate (BEC). Cataliotti *et al.* (p. 843) trapped a BEC in an array of optical potential wells so that the barrier height between wells could be controlled. A collective oscillatory motion of the atoms was observed between wells that is a signature of the Josephson effect.



CREDIT: CATALIOTTI *ET AL.*

Sticklers About the Time

High-precision atomic clocks keep time by counting the number of transitions between the hyperfine levels of atomic cesium. Higher frequency standards in the optical range would provide finer time intervals (femtoseconds versus roughly tenths of nanoseconds) that would not only provide greater precision for time metrology but could also help constrain important physical constants, such as the fine structure constant and the Rydberg constant. Building on recent technological advances in generating optical-frequency combs, measuring absolute optical frequencies, and trapping and cooling single ions to extremely low temperatures, Diddams *et al.* (p. 825) developed an optical clock based on an ultraviolet transition of a single trapped mercury ion. They demonstrate time precision better than that of existing atomic-clock standards.

The Lowdown on Noses

Nostrils and noses, and more generally the role of smell and extent of air exchange, play a large role in the behavior of many vertebrates. Understanding the role that smell played in dinosaur behavior has been problematic because of the lack of direct fossil evidence for these fleshy structures. Witmer (p. 850; see the cover and the news story by Stokstad) has made comparisons of nostril positions in living animals to conclude that dinosaur noses were not located to the rear of the bony nasal opening and high on the face, as has been generally thought, but low on the face just above the upper jaw. This position now seems to apply generally across reptiles, birds, and mammals.

Ironed Out

Iron is an essential element in regulating marine phytoplankton growth, and even where iron is present, its bioavailability depends on whether it exists in dissolved form, which is easy for algae to utilize, or as a colloid, which is much less readily used. Wu *et al.* (p. 847) used a new analytical technique to measure vertical profiles of iron speciation in oligotrophic waters of the North Atlantic and central North Pacific. Much of the iron in these waters (up to 90%) that was previously believed to be dissolved is actually colloidal. The limitation of nitrogen fixation by iron is apparently much more important than had been realized previously.

Death by Deprivation

Many hematopoietic cells die by apoptosis when deprived of specific cytokines, and this process requires active transcription. Using DNA microarrays to identify specific genes that are transcriptionally activated after cytokine withdrawal, Devireddy *et al.* (p. 829) discovered an important new player in this cell death pathway. In a study of interleukin-3 (IL-3)–dependent murine FL5.12 pro-B cells, they find that the gene showing maximal transcriptional activation upon IL-3 withdrawal is *24p3*. The *24p3* gene encodes a small secreted protein with sequence motifs characteristic of lipocalins, a large family of proteins previously linked to diverse functions ranging from retinol transport to prostaglandin synthesis to modulation of the immune response. Addition of 24p3 to the culture medium induced apoptosis of a wide variety of leukocytes, and apoptotic sensitivity appeared to be determined by the presence or absence of a cell surface receptor for 24p3.

Dicing Developmental RNA

Small noncoding RNAs, such as the ~21 nucleotide (nt) *let-7* RNA, regulate the developmental timing of the nematode *Caenorhabditis elegans*. These RNAs are highly conserved in many bilaterally symmetrical organisms, including humans. The similarity in size between the *let-7* RNA and those generated during RNA interference (RNAi), in which RNA blocks gene expression, has led to the suggestion that the two may be linked. Hutvágner *et al.* (p. 834; see the Perspective by Ambros) now show that the enzyme Dicer, which is implicated as the ribonuclease involved in the generation of the small 21- to 23-nt interfering RNAs in RNAi, is also responsible for cleaving the putative ~70-nt *let-7* precursor to generate the *let-7* RNA.

A Matter of Timing

Covalent modification of the amino-terminal tails of the core histones (H2A, H2B, H3, and H4), the proteins that make up the bulk of chromatin in eukaryotes, play an important role in modulating chromatin function. For example, acetylation of histone tails plays a role in transcription, and phosphorylation has been implicated in

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CONTINUED ON PAGE 759

STEREO MICROSCOPES

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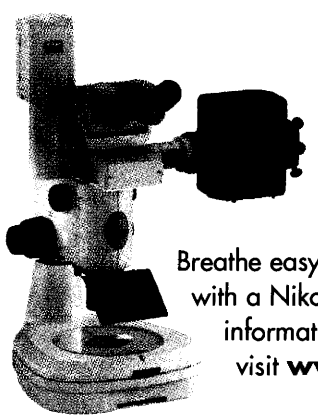

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chromosome condensation. The role of histone methylation has been less well characterized. Wang *et al.* (p. 853) now show that the enzyme PRMT1 (a protein arginine methyltransferase) methylates the Arg3 residue in H4 tails in vivo. Methylation of Arg3 enhances subsequent acetylation at lysine residues 5, 8, 12, and/or 16 by the histone acetyl-transferase p300, but prior acetylation of these residues inhibits methylation, which suggests that the different modifications are coordinated temporally. Furthermore, H4 methylation facilitates the activation of transcription, providing further evidence for a histone "code."

News from the Resistance

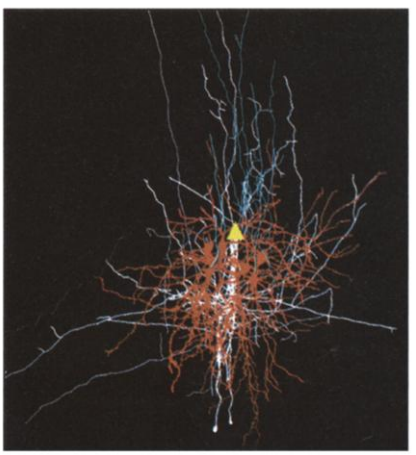
The commercialization of transgenic plants that express toxins from *Bacillus thuringiensis* (Bt) has spurred a number of groups to search for the genes responsible for resistance (see the news story by Stokstad). Gahan *et al.* (p. 857) combined genetic mapping in a laboratory-generated resistant strain with knowledge of Bt-binding proteins in other species and identified a member of the cadherin superfamily, HevCaLP, as a candidate resistance gene in the tobacco budworm. Griffitts *et al.* (p. 860) have harnessed the power of genetic analysis in the model organism *Caenorhabditis elegans* to show that lack of expression of a gene encoding a potential β-1,3-galactosyltransferase in the intestine resulted in resistance to the Cry5B toxin.

A Repeated Theme

The causative genetic defect of myotonic dystrophy (DM1) was identified in 1992 as an expansion of a CTG repeat in the 3′ untranslated region of the dystrophia myotonica-protein kinase gene (*DMPK*) on chromosome 19q. Subsequent genetic testing revealed the existence of a clinically similar but genetically distinct form of DM, DM2, linked to chromosome 3q. Liquori *et al.* (p. 864; see the Perspective by Tapscott and Thornton) now show that DM2 is also caused by expansion of a repeat sequence in a noncoding region of a gene, specifically, a CCTG repeat in intron 1 of the *zinc finger protein 9* gene. This discovery provides compelling support for the hypothesis that repeat expansions expressed only at the RNA level can be pathogenic.

Neocortical Building Blocks

Is there precise connectivity in the highly complex neocortex, or do neurons make random contacts with each other? Kozloski *et al.* (p. 868) addressed this problem by applying a new method for identifying connected neuronal pairs. They observed extreme specificity among local synaptic circuits in layer V of the primary visual cortex. Cells strongly activated by corticotectal pyramidal neurons fell into a small subset of the many cell types found in this cortical layer, and the relative position of these targeted neurons appeared determined in different animals. The authors suggest that these stereotyped cortical microcircuits are controlled by early events during neocortical development.



CREDIT: KOZLOSKI *ET AL.*

The Appearance of Drug Resistance

STI-571 is a new cancer drug that has shown remarkable efficacy in patients who are in the early stages of chronic myeloid leukemia (CML). The drug inhibits the Abl kinase, which is constitutively activated in CML patients because they carry a characteristic chromosomal translocation that fuses the *ABL* gene with the unrelated *BCR* gene. Patients in whom CML has progressed to a stage called blast crisis respond to STI-571 initially, but then develop resistance. Gorre *et al.* (p. 876; see the 22 June news story by Marx) studied nine patients who had relapsed after STI-571 treatment and found that all nine showed reactivation of the Bcr-Abl signaling pathway. Six patients had acquired the same amino acid substitution in the Abl kinase domain—a change predicted to alter interaction of the kinase with the drug—and the other three showed *BCR-ABL* gene amplification. Identification of the mechanisms responsible for STI-571 resistance may facilitate the design of next-generation drugs for CML.

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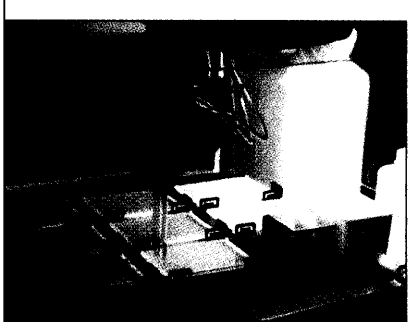

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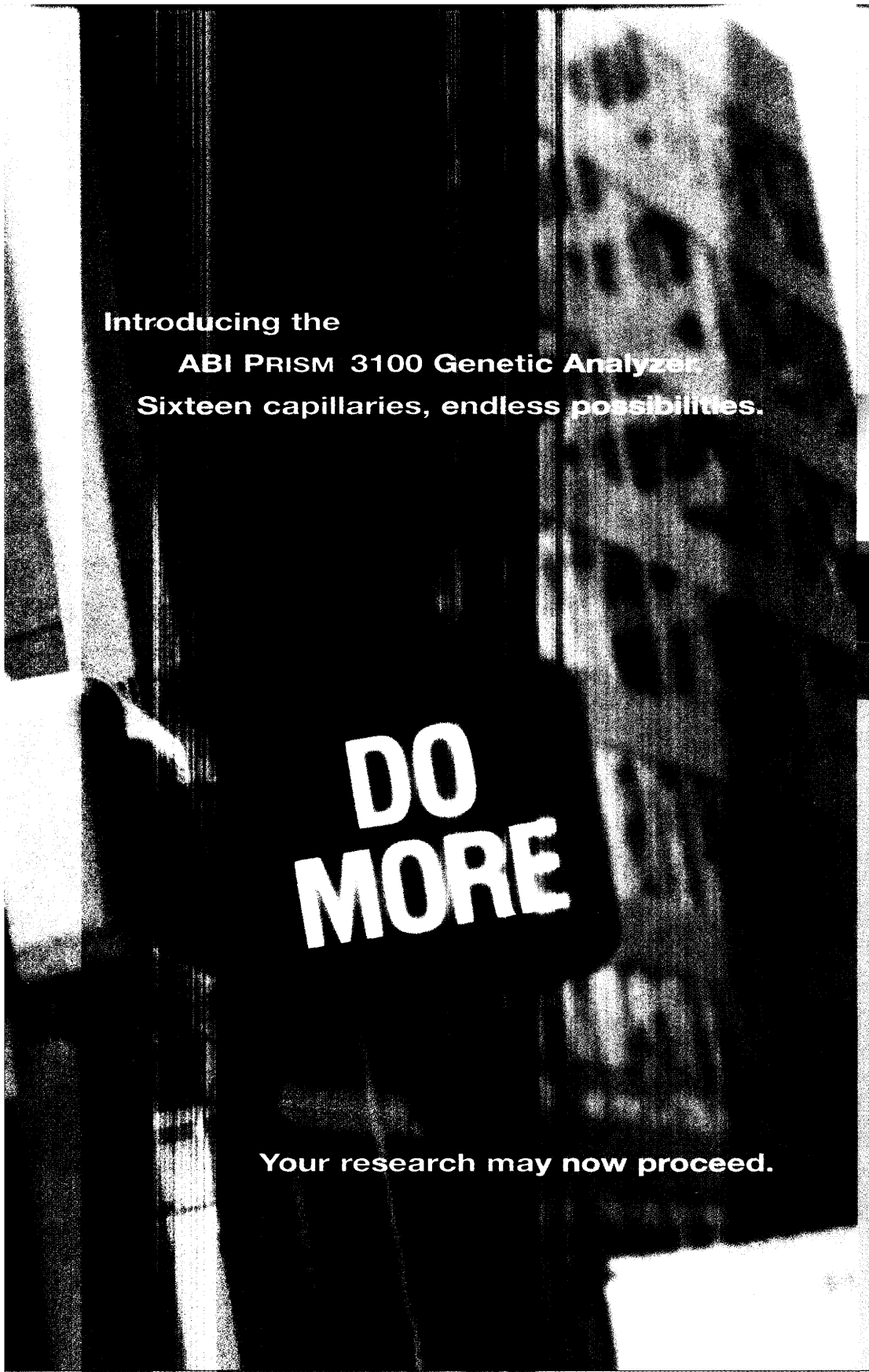

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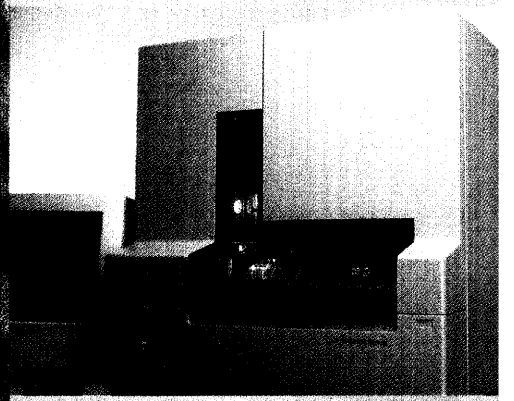

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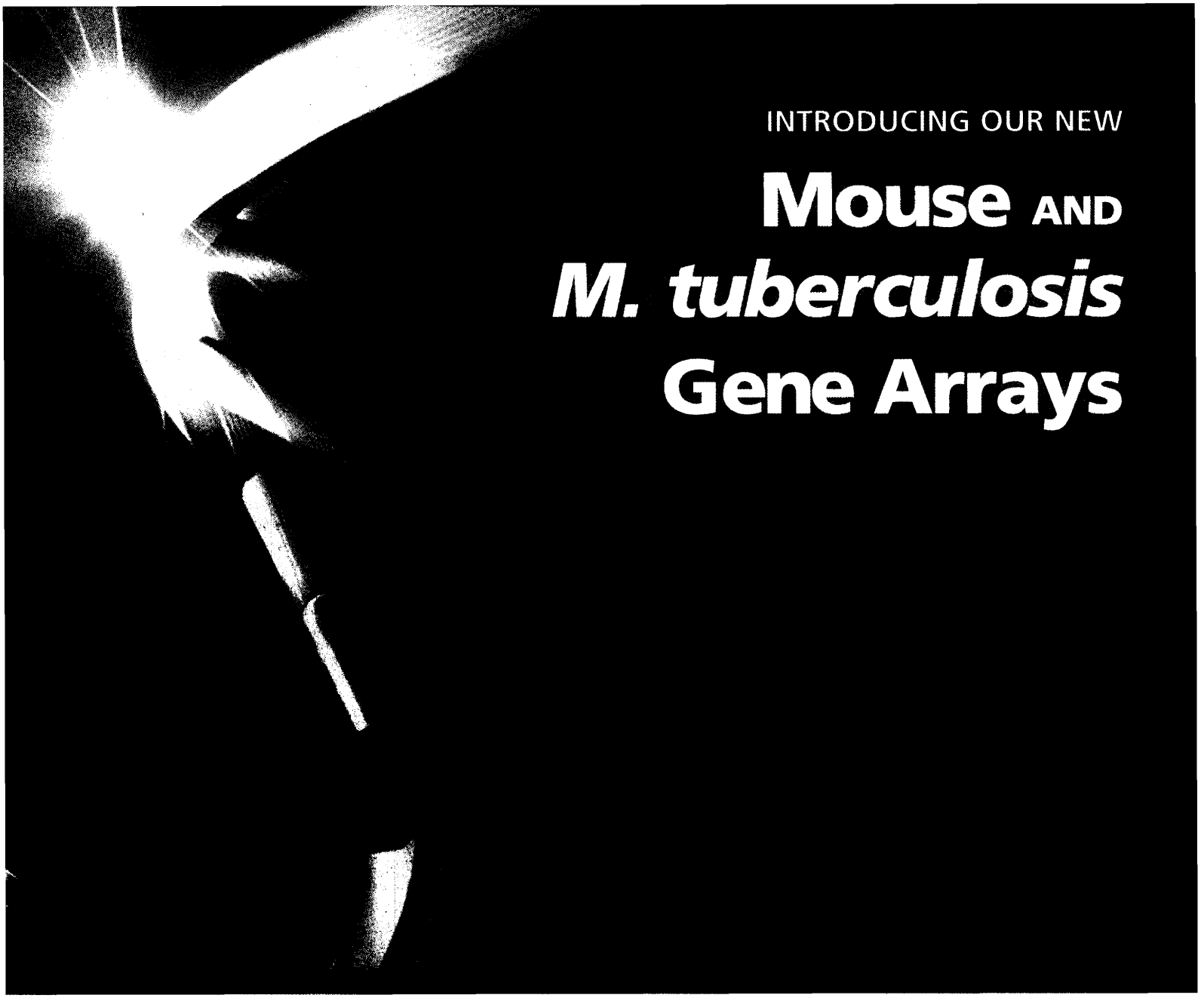

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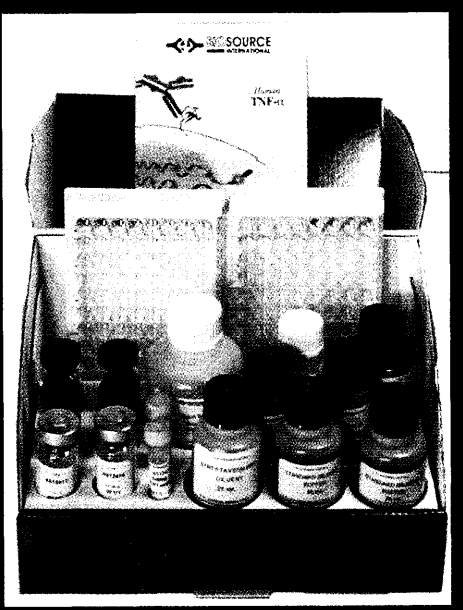

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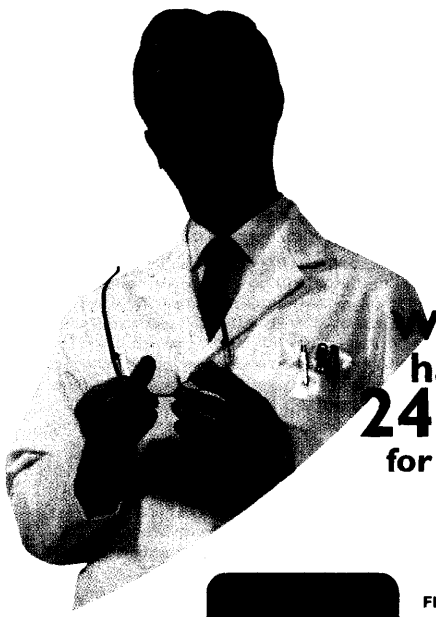

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FIG. 1 Cells are not fixed

Actin filament labeling of human fibroblast (HS68) cells using anti-actin antibody delivered by CHARIOT. (65% transfection efficiency)

FIG. 2 Cells are fixed

FIG. 3 CHARIOT delivery of a 10 kDa protein, labeled with lucifer yellow at the C-terminus, to the nucleus of human fibroblast (HS68) cells. Cells are not fixed. (70% transfection efficiency after 30 min. incubation)

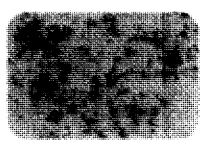

FIG. 4 CHARIOT delivery of a 119 kDa β-galactosidase protein into COS cells. Cells are fixed and stained 2 hours post-transfection. (60% transfection efficiency)

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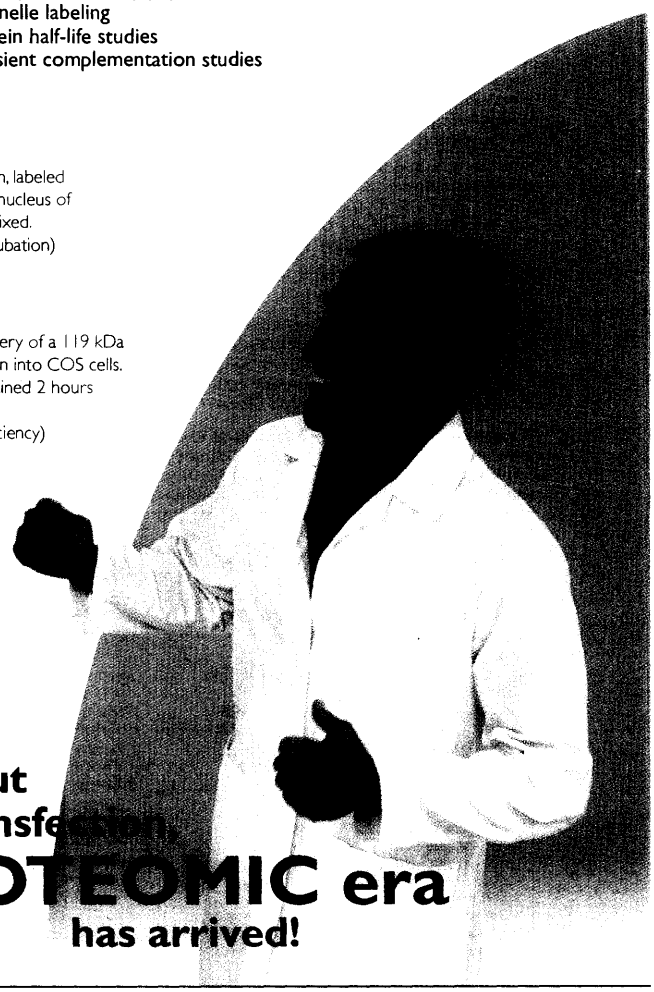

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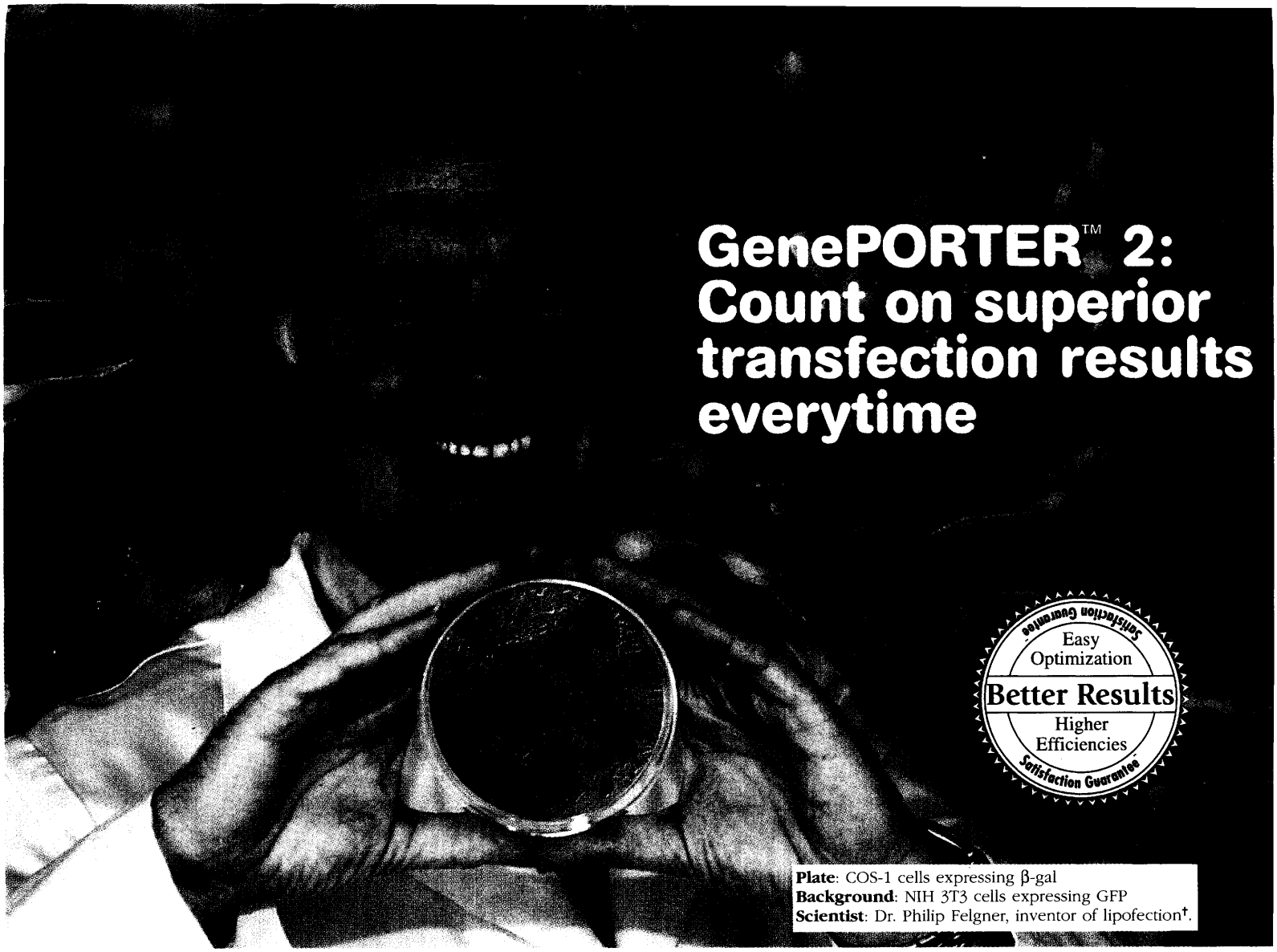

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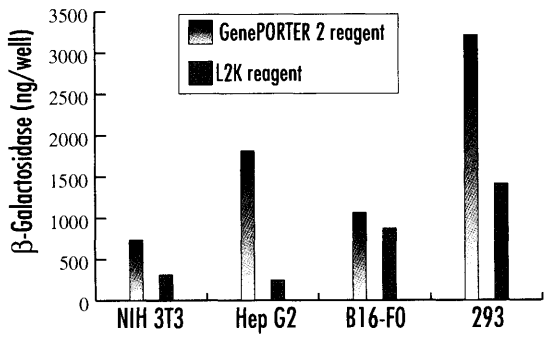

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Fig. 1. Fluorescent sequencing results of a 100 bp pUC18 PCR fragment sequenced with a -20 Fwd primer using the DYEnamic ET Terminator Cycle Sequencing Kit (Amersham Pharmacia Biotech). Data generated for USB by Cleveland Genomics (clevelandgenomics.com), a research service company. PCR clean-up performed with: (a) ExoSAP-IT; (b) a column designed for PCR clean-up. Base miscalls in (b) are due to inherently low yields of short PCR products when using columns.

Fig. 2. Autoradiograms of a 20.7 kb Lambda PCR fragment sequenced with MBL202 Fwd primer using USB's Thermo Sequenase Radiolabeled Terminator Cycle Sequencing Kit. PCR clean-up performed with: (a) ExoSAP-IT; (b) a column designed for PCR clean-up.

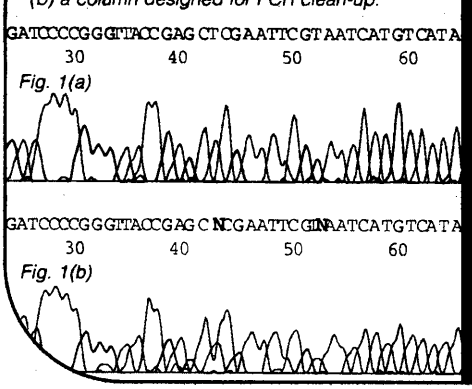

Fig. 1(a)

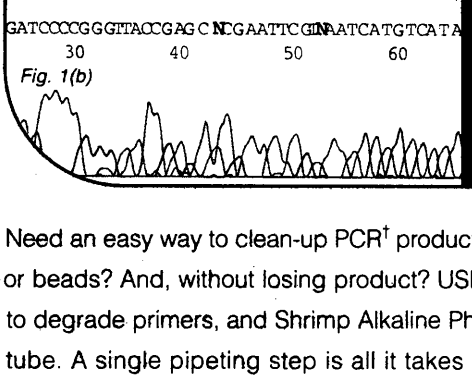

Fig. 1(b)

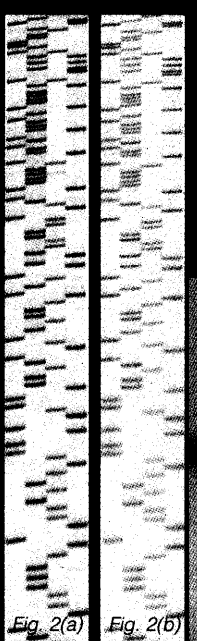

Fig. 2(a) *Fig. 2(b)*

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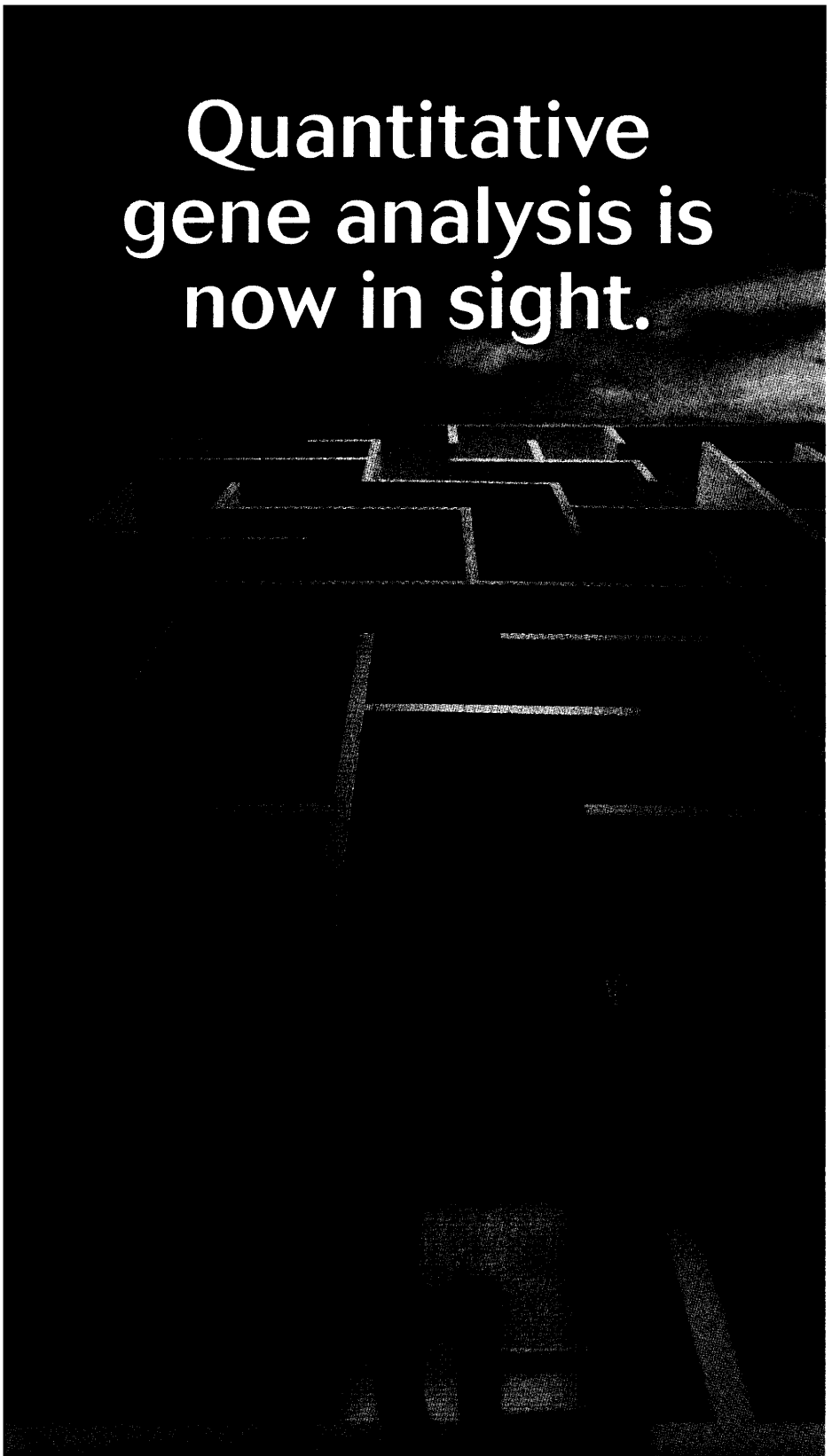

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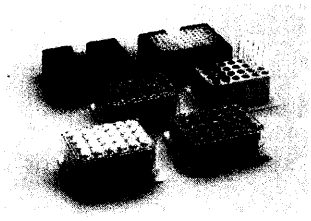
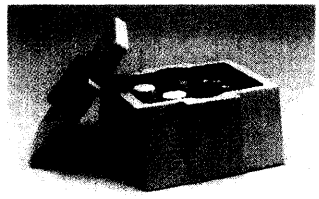
The perfect insulation of the thermoblocks guarantees precise temperature control. What is more, there is no risk of burns to users' hands as the tubes can be removed easily at all times, even during the temperature-control process. Of the six exchangeable thermoblocks which can be used with the ThermoStat plus, five have the same design as those for the Eppendorf Thermomixer comfort. Another compatible partner is the IsoTherm-System® with its tailor-made racks and cool packs. And the universal CombiBox thermoblock transforms the ThermoStat plus into a temperature-stable reagent depot, with space for individual tubes with a height of up to 60 mm.
Eppendorf ThermoStat plus: A red-hot tip for every lab!





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- Exchangeable thermoblocks:
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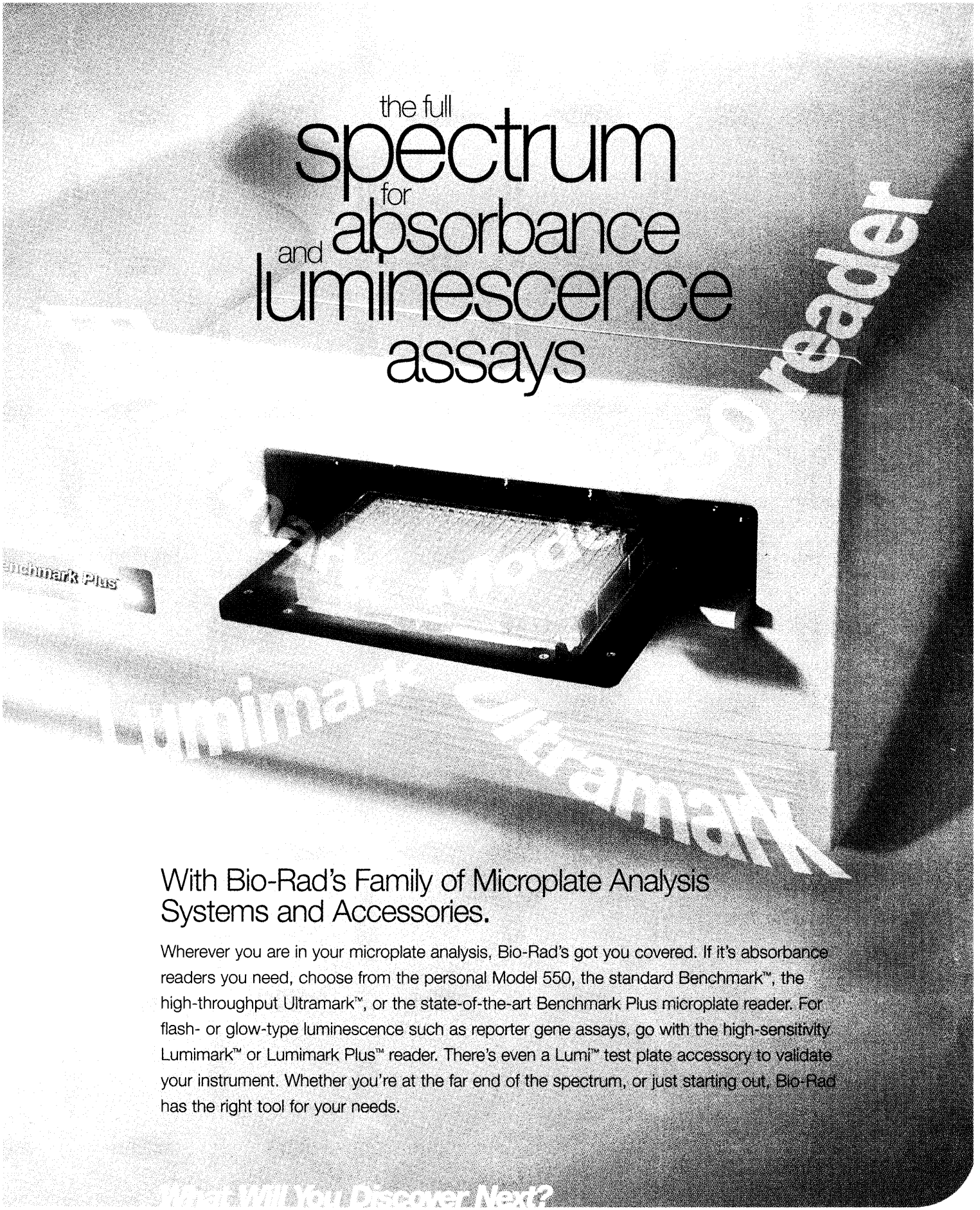

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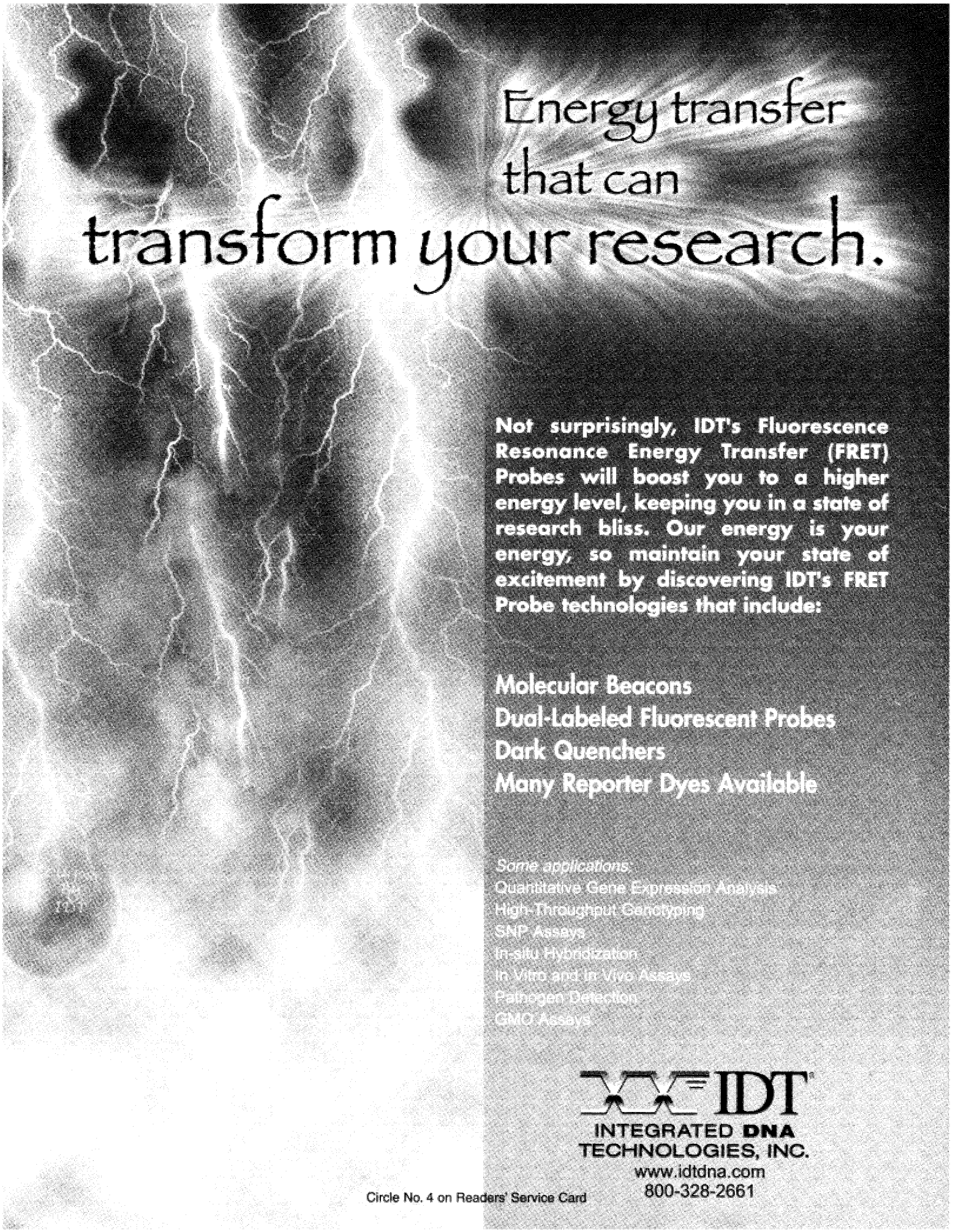

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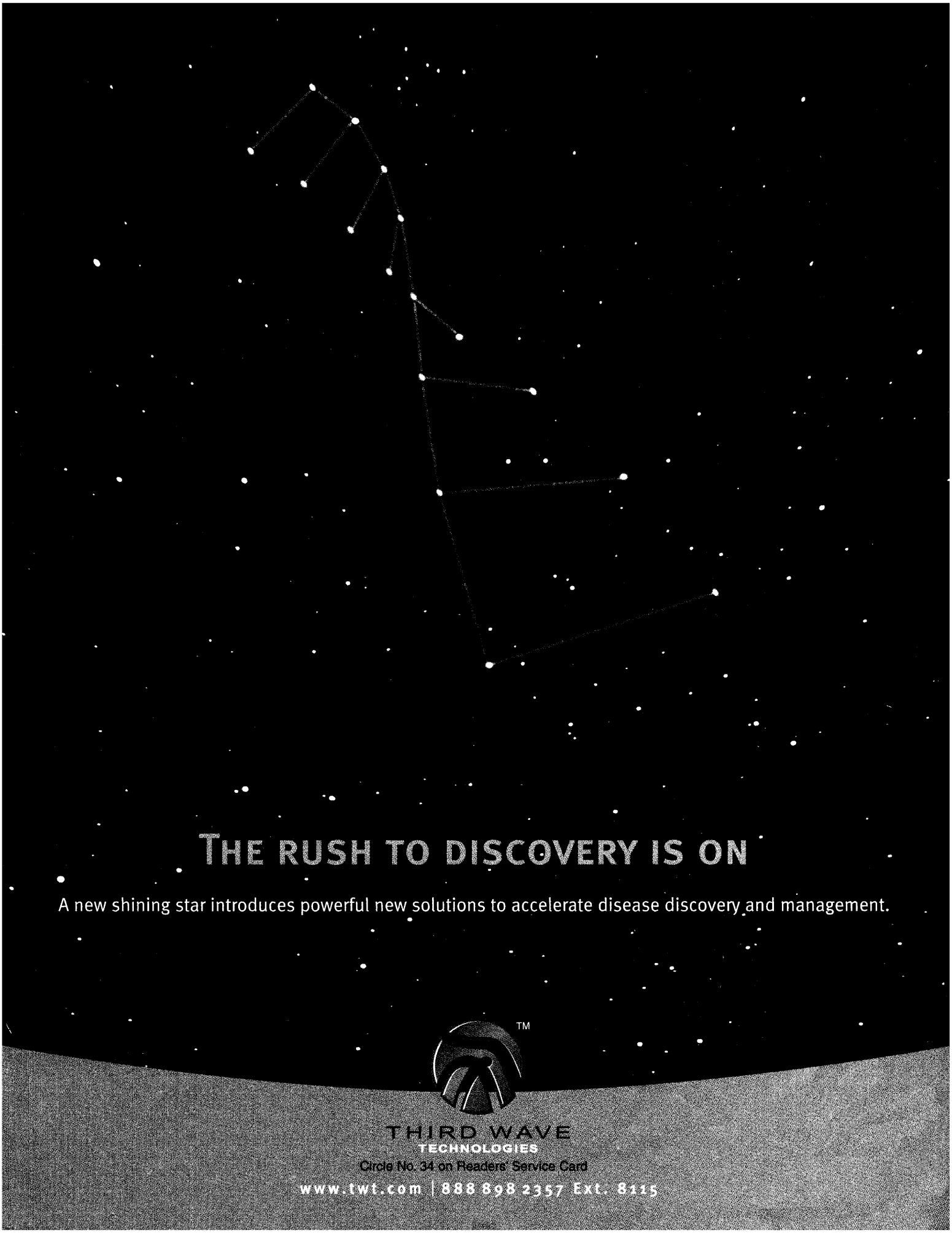
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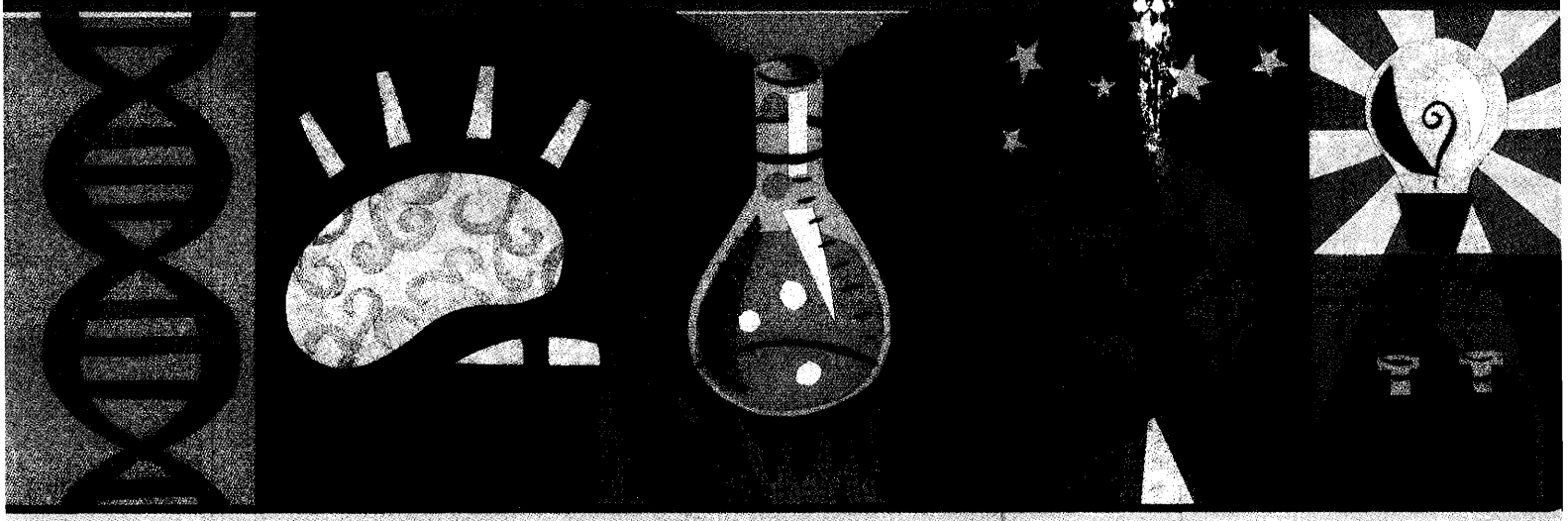

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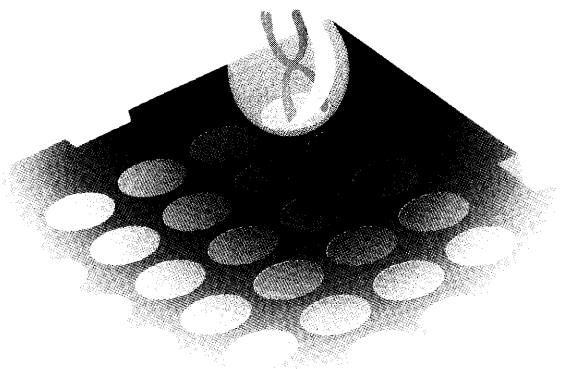

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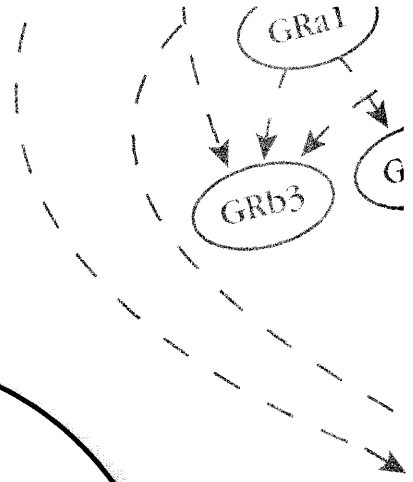
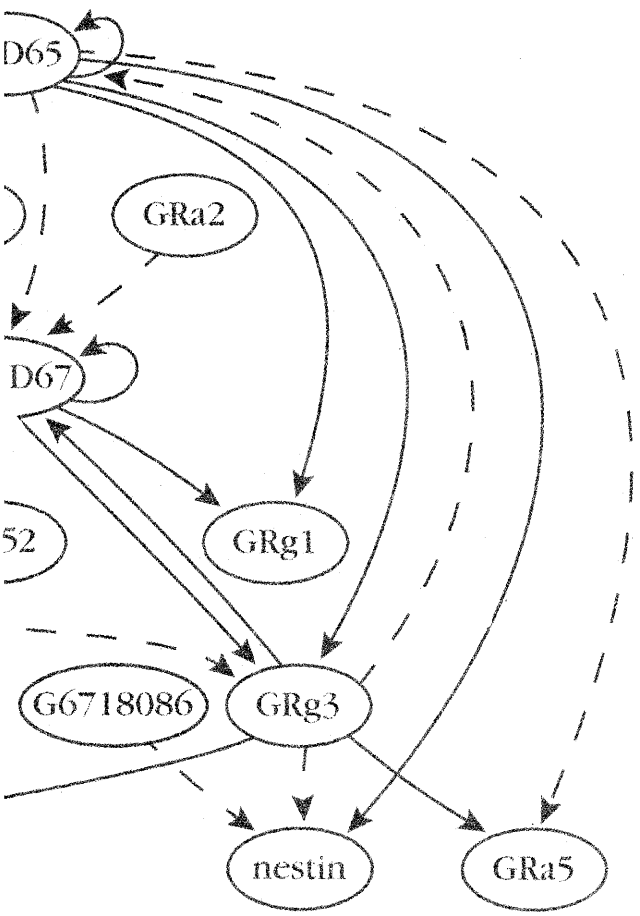
Gregor Mendel didn't make the rules. He just helped explain them.





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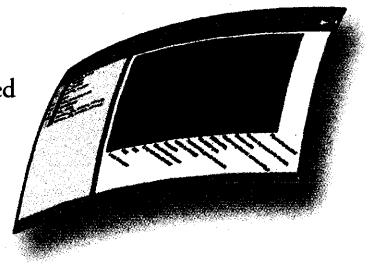

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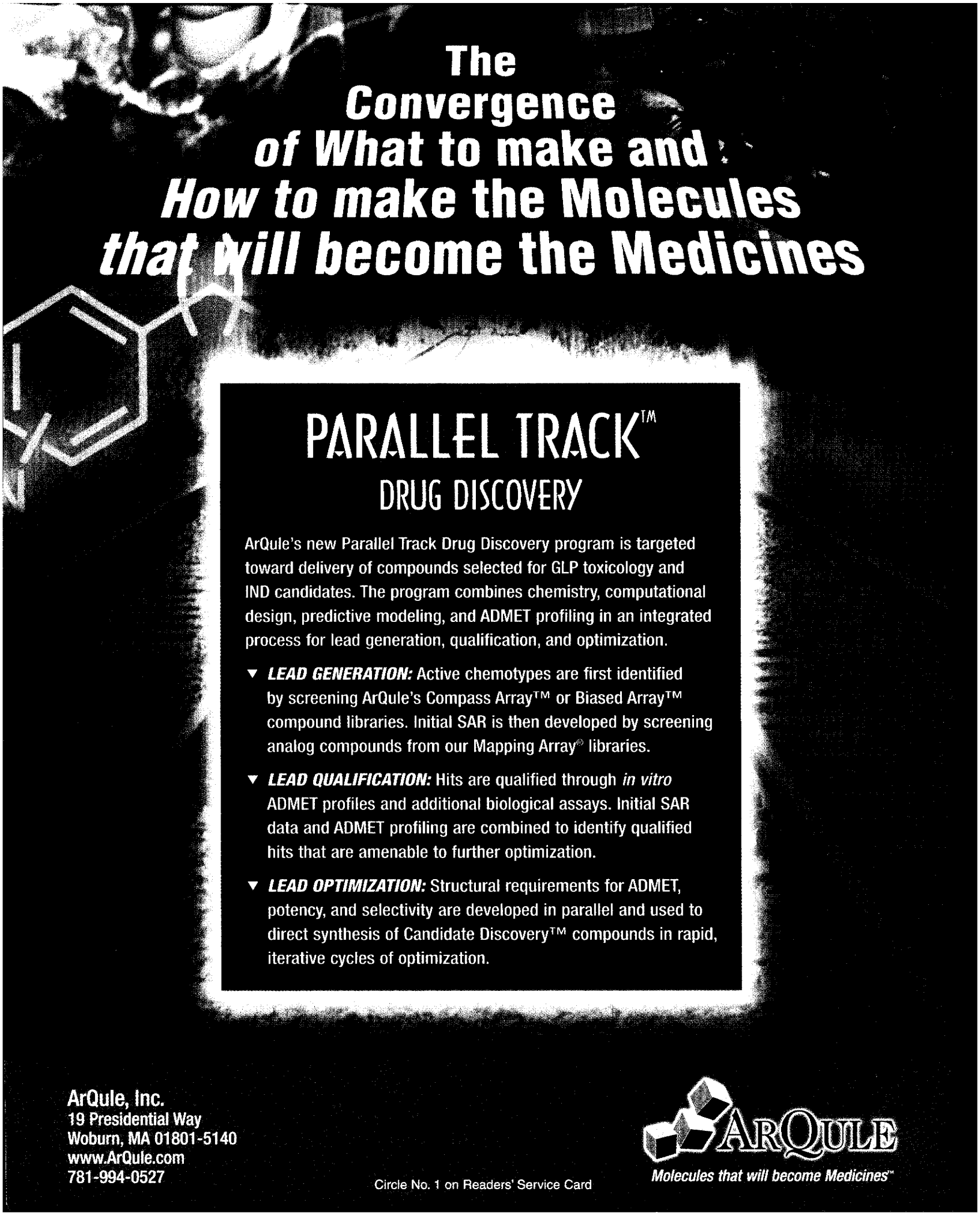
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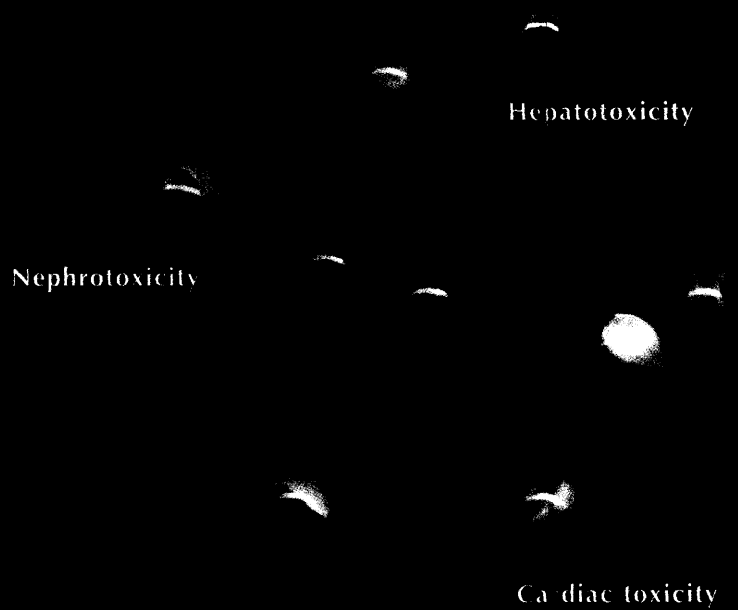

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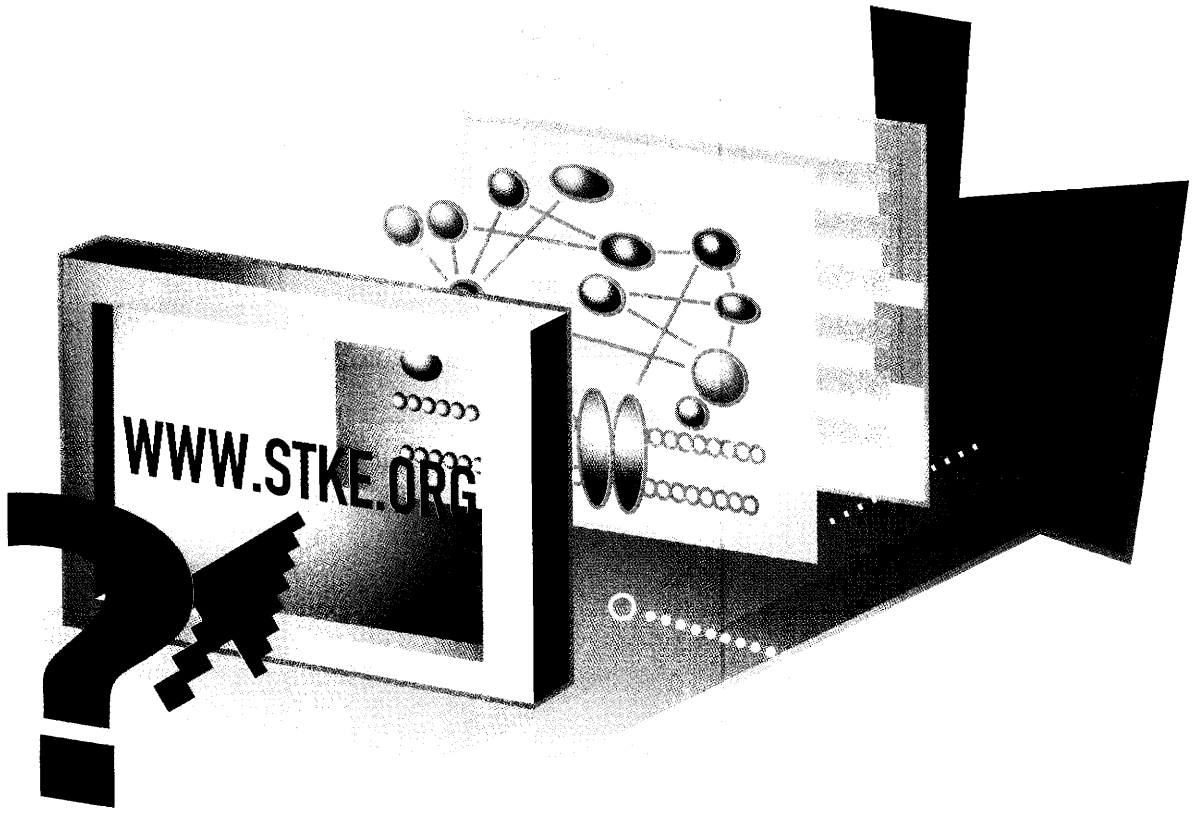

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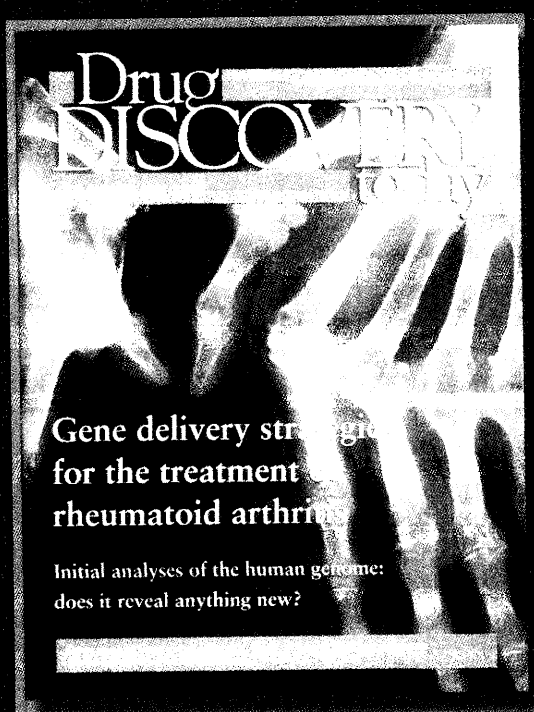

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