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Vaccines and Immunity

American Association for the Advancement of Science

Science

Volume 293 **13 July 2001** **Number 5528**

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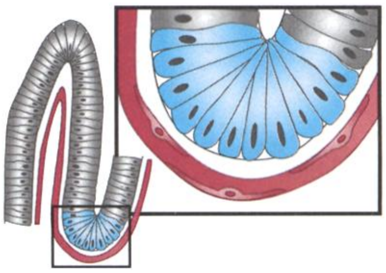

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Endothelial cells take center stage

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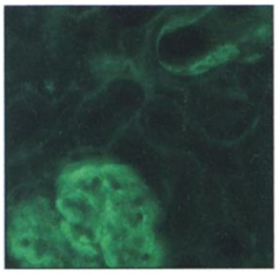

COVER 233

Abnormal immunoglobulin deposits (green fluorescence) in a kidney glomerulus of a mouse with mutations in the genes encoding the closely related receptor tyrosine kinases Tyro 3, Axl, and Mer. These mice develop a severe lymphoproliferative autoimmune disease and generate self-reactive antibodies that attack a variety of tissues, including the kidney. [Image: Q. Lu, G. Lemke]

RESEARCH

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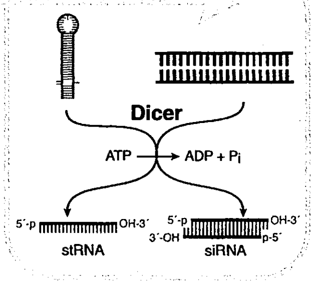
Signaling from a distance

New on *Science* Express A common mechanism for stRNA and RNAi



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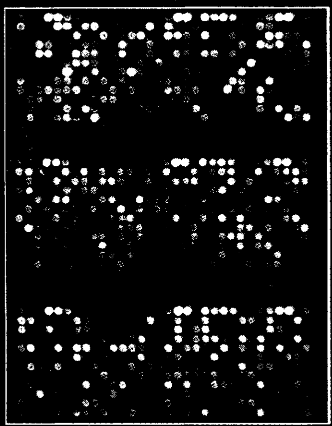

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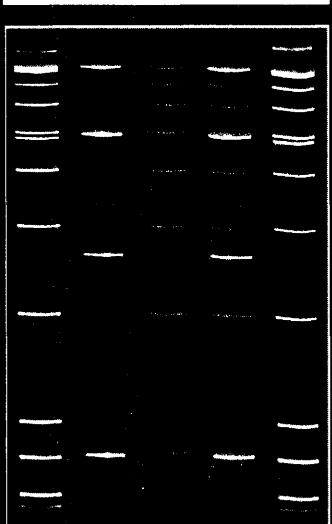

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An Optical Clock Based on a Single Trapped $^{199}Hg^{+}$ Ion
S. A. Diddams *et al.*

An all-optical clock based on the high-frequency transitions of a single mercury ion shows better precision than existing atomic-clock time standards.

Crystal Structure of Sensory Rhodopsin II at 2.4 Å: Insights into Color Tuning and Transducer Interaction H. Luecke, B. Schobert, J. K. Lanyi, E. N. Spudich, J. L. Spudich

How to convert a green light–absorbing transporter of protons and chloride into a sensor that mediates avoidance of blue light.

A Cellular Function for the RNA-Interference Enzyme Dicer in the Maturation of the *let-7* Small Temporal RNA G. Hutvágner *et al.*

The enzyme Dicer, which generates the small ~22-nucleotide RNA fragments crucial for RNA interference, also cleaves and generates the small temporal RNA *let-7*, which is vital for development.

Haplotype Variation and Linkage Disequilibrium in 313 Human Genes J. C. Stephens *et al.*

Detailed analysis of 3899 single-nucleotide polymorphisms in genes from 82 unrelated individuals provides a foundation for future studies of human disease, population genetics, genomic variability, and evolution.

SPECIAL FEATURES

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Perspective: Slit—A Roadblock For Chemotaxis A. Z. Fernandis and R. K. Ganju

Another example of signals used by both the nervous system and the immune system.

Perspective: A Call to Arms—The Cytokine Selection Service J. W. Nelson

Cytokines influence the survival and proliferation of newly differentiating helper T cells.

Connections Map: T Cell Signal Transduction Pathway Authorities: G. A. Koretzky and A. L. Singer

From T cell receptor engagement to transcriptional regulation.

science's next wave www.nextwave.org

Canada: Training Tomorrow's Professors L. McKarney

The University of Alberta gives its graduate students the opportunity to acquire teacher training . . . and then gives them credit for it.

US: Alone in Good Company J. Austin

Northwestern University's first tenured female chemist, Hilary Arnold Godwin, talks to Next Wave's Career Development Center about research, tenure, and family.

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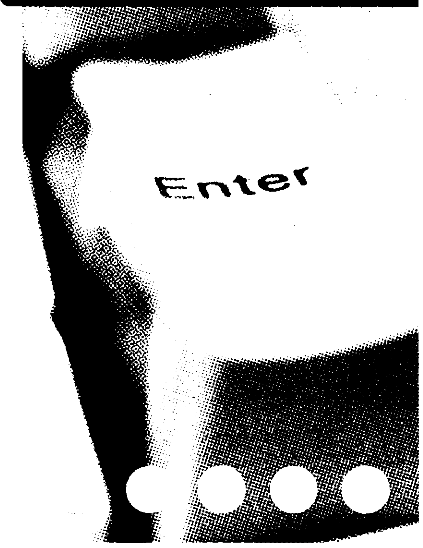


THIS WEEK IN Science

edited by Phil Szuromi

Found in the Ozone

Recombination of oxygen atoms and oxygen molecules in the upper atmosphere can form ozone, and this process leads to enrichments in the isotopes ^{17}O and ^{18}O by approximately the same amount above their natural abundances. This effect is puzzling, because standard chemical wisdom would predict the enrichment of ^{18}O should be about twice as great as that of ^{17}O. Under other conditions, however, extremely large mass-dependent fractionation has been observed. Gao and Marcus (p. 259; see the Perspective by Thiemens) present a theoretical description of the transition state dynamics for this reaction that can explain why both mass-independent and mass-dependent oxygen isotope fractionation can be observed for ozone synthesis under different conditions. ℰX

278 Single-Atom Delivery on Demand

The manipulation of single-quantum objects is a key requirement for the engineering of microscopic quantum systems. Applications such as single-atom micromasers (microwave lasers), triggered single-photon sources, or deterministic entanglement of atoms all require the ability to deliver single atoms on demand to a desired location. The trapping and manipulation of atoms as neutral species is more challenging than for charged ions because of the weak interaction of neutral species with electromagnetic fields. Kuhr *et al.* (p. 278) have overcome these difficulties by combining magneto-optical trapping and optical-trapping techniques. They demonstrate the precision transport of single neutral cesium atoms over distances of 1 centimeter and the ejection of single atoms into free flight. ℰX

A Trick Shot in Quantum Billiards

When a cloud of atoms is cooled and held in an optical trap and then allowed to cool again, the trajectories of the atoms will depend on the geometry of the confining walls imposed by light beams. Most trajectories will be chaotic, but some geometries exist in which the scattering processes satisfy momentum-selection rules that give rise to stable trajectories. Steck *et al.* (p. 274; see the Perspective by Habib), using a system in which the atoms are confined in an optical standing wave and using a velocity-selection technique, show that for special regions of momentum space, termed "islands of stability," the atoms can tunnel between one stable momentum state and its symmetric opposite. Time-slice measurements show that the atoms oscillate between the two stable momentum states. ℰX

Faster Route to Fatty Acids

In eukaryotic cells, the synthesis of polyunsaturated fatty acids (PUFAs), lipids that are critical for generating cellular membranes and signaling molecules, requires numerous steps by several enzymes to generate carbon-carbon double bonds. Metz *et al.* (p. 290) show that in certain marine prokaryotes and protists, a more simplified scheme is at work. These microrganisms can produce PUFAs through the action of a single enzyme called polyketide synthase. These enzymes may prove useful in the synthesis of new anitbiotics.

Boron in Magmas

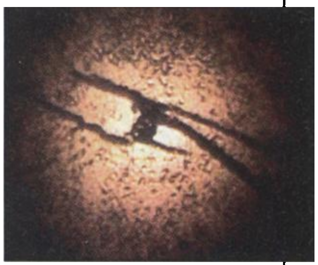
Subduction of a crustal plate leads to the formation of a volcanic arc, but the processes that generate the volcanoes' magmas remain poorly understood. Rose *et al.* (p. 281) used the concentration and the isotopic characteristics of boron from melt inclusions trapped in olivine phenocrysts in basaltic lavas from Mount Shasta, California, to evaluate the melt process. The melt inclusions contain a low concentration of isotopically light boron. Dehydration of the subducting slab would reduce the amount of boron left in the slab residue. This residue may be re-equilibrated with the surrounding rocks and melted to produce the Mt. Shasta lavas.

Parkinson's Disease Comes Together

The cause of most cases of Parkinson's disease, a neurodegenerative disorder, is not known, but in a few families that show clear inheritance of the disease, a mutation in one of three genes results in symptoms. Shimura *et al.* (p. 263; see the Perspective by Haass and Kahle) show that the products of two of those genes, parkin and α-synuclein, functionally interact in the cell. Parkin, a ubiquitin ligase that tags other proteins for degradation, favors a substrate that is a p21 isoform of α-synuclein. When mutated, parkin cannot bind to or add ubiquitin to the synuclein isoform, and so the isoform builds up in the cell. The authors suggest that this overabundance of synuclein isoform causes the Parkinsonian degeneration. ℰX

Squeezing Superconductivity into Boron

Although theory has suggested that boron should superconduct at high pressure, conductivity measurements are difficult to make at very high pressures and cryogenic temperatures. Eremets *et al.* (p. 272; see the Perspective by Geballe) show that boron does indeed transform into a superconductor with a transition temperature of 6 K at a pressure of 175 gigapascals and 11.2 K at 250 gigapascals. A phase transition that changes the bonding in boron might accompany the onset of the superconducting transition.



Sending Messenger RNA Messages

Certain plant viruses propagate their infection via the intercellular transport of the viral RNA molecule. Kim *et al.* (p. 287) now show that endogenous messenger RNA (mRNA) molecules in noninfected plants not only travel between cells, but also may execute their developmental functions in cells far removed from those in which the RNAs were transcribed. Grafts between tomato plants with normal and mutant leaf shapes show that mRNA from the mutated gene responsible for the altered leaf shape can

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CONTINUED ON PAGE 171

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travel from the mutant graft stock into the wild-type graft scion and alter leaf shape in the otherwise genotypically wild-type scion. The promotion of mRNA from intracellular to intercellular information conduit complicates views of developmental regulation.

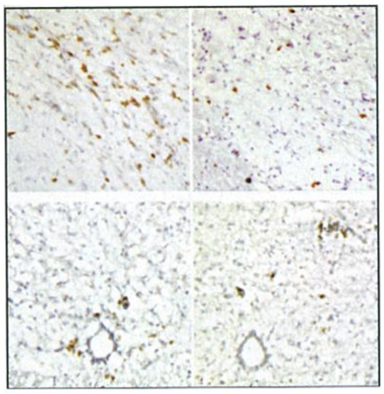
Cryptic Damage

Injury to the gastrointestinal (GI) tract limits the use of radiation for the treatment of cancer. According to the prevailing hypothesis, this so-called "GI syndrome" arises because radiation therapy directly damages the epithelial stem cells within the intestinal crypts of Lieberkühn and causes their clonogenic death. Paris *et al.* (p. 293; see the Perspective by Folkman and Camphausen) argue that the actual target of radiation damage is the intestinal microvascular endothelial cells. Using mouse models, they found that pharmacological inhibition of GI endothelial apoptosis prevented radiation-induced crypt damage, organ failure, and GI death. Thus, it may be possible to reduce radiation damage to the bowel by administering endothelial survival factors such as basic fibroblast growth factor.

Divergent Interferon Signaling

Two tools used by the immune system to fight viruses and bacteria are the interferons IFNα/β and IFNγ. These cytokines induce the transcription of antiviral and antibacterial response genes via the recruitment of signal transducer and activator of transcription (STAT)–1 proteins. In a study of a naturally occurring mutations, Dupuis *et al.* (p. 300) show that STAT-1 may direct immunity to viruses and bacteria through distinct pathways. A mutation that diminished phosphorylation of a specific tyrosine residue acted in a dominant-negative fashion to prevent the nuclear translocation of homotypic STAT-1 transcriptional complexes. In turn, this mutation correlated with a severe impairment of immune responses of individuals carrying the mutation to nonvirulent forms of mycobacteria. Remarkably, the same mutation did not affect viral immune responses and correlated with relatively normal nuclear translocation of a second heterotrimeric complex involving STAT-1.

Viruses Get Nervous



Infection with certain neurotrophic viruses can cause chronic encephalitis and progressive neurologic disease. Although B cells have been shown to clear alphavirus from neurons, less information is available on mechanisms by which T cells participate in viral clearance. In a study of a Sindbis virus infection model, Binder and Griffin (p. 303), observed that mice lacking the capacity to mount a B cell response could nevertheless clear the virus from neurons within the spinal cord and brain stem but not from cortical neurons. This T cell dependent clearance was recapitulated in the absence of both B and T cells by using recombinant viruses that express interferon γ. Distinct mechanisms appear to be important in the selective immune clearance of virus from populations of neurons in the central nervous system.

Pain, Emotion, and Engogenous Opioids

The μ-opioid receptors are implicated not only in the action of opiate drugs but also help mediate stress and pain. In a positron emission tomography study, Zubieta *et al.* (p. 311) investigated normal human volunteers during episodes of experimentally induced and controlled pain. They detected significant endogenous opioid release and interaction with μ-opioid receptors in the contralateral thalamus, hypothalamus, and insula, in the ipsilateral amygdala, and bilaterally in the cingulate cortex and prefrontal cortex. They also found direct evidence for the role of μ-opioid receptors in the regulation of the individual subjective experience of pain. Thus, the endogenous opioid system, through the activation of μ-opioid receptors in specific brain regions, is involved in the attenuation of sensory and pain-specific emotional responses.

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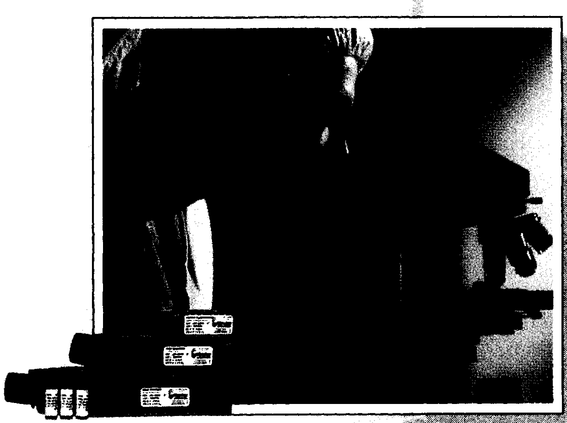

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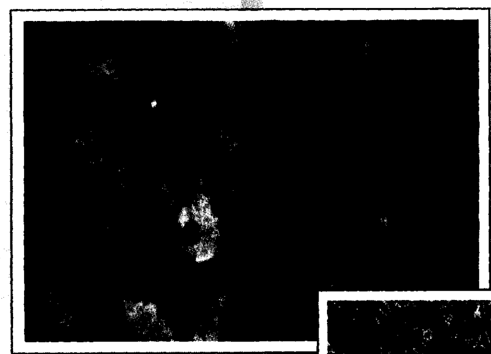

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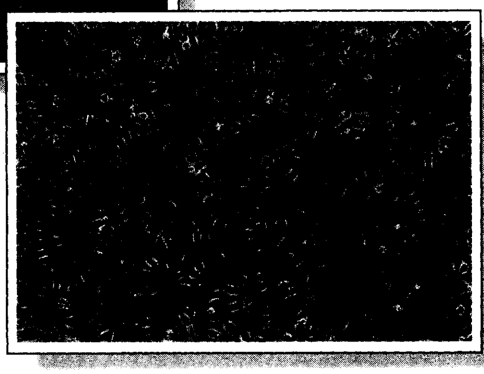

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- Dermal, Lung, Microvascular
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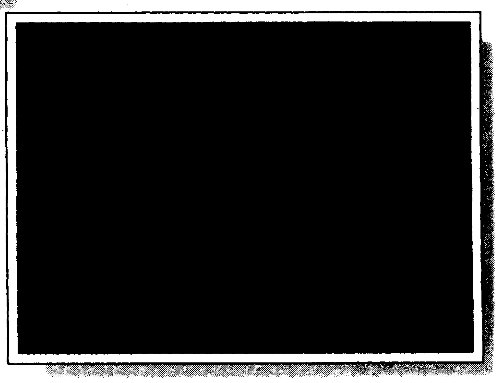


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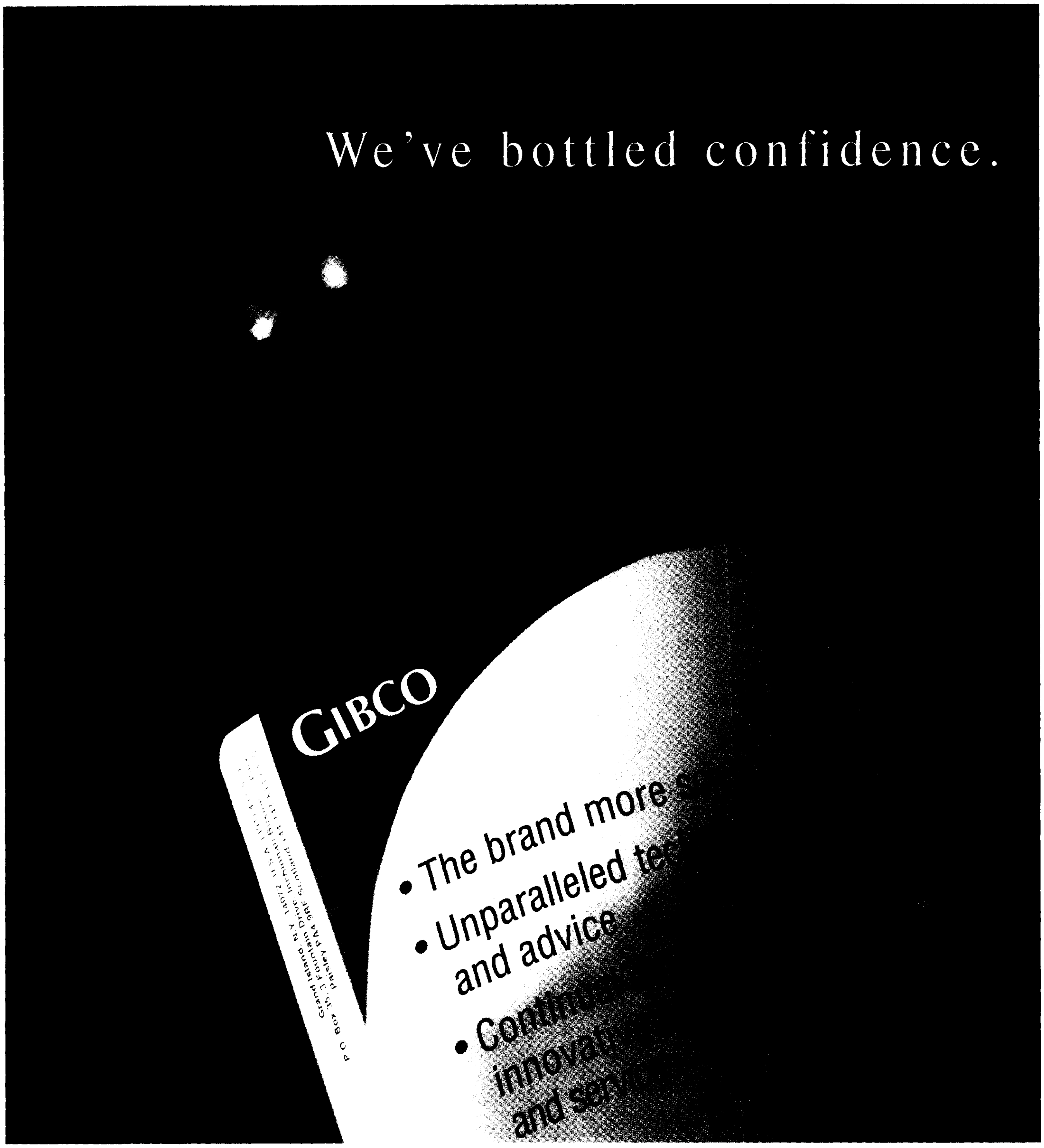
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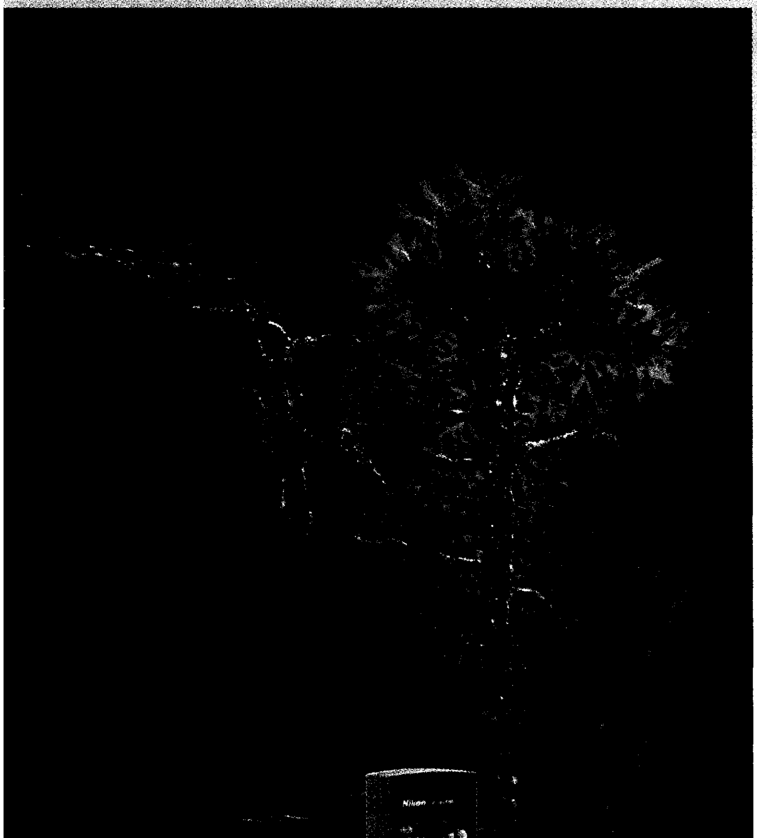

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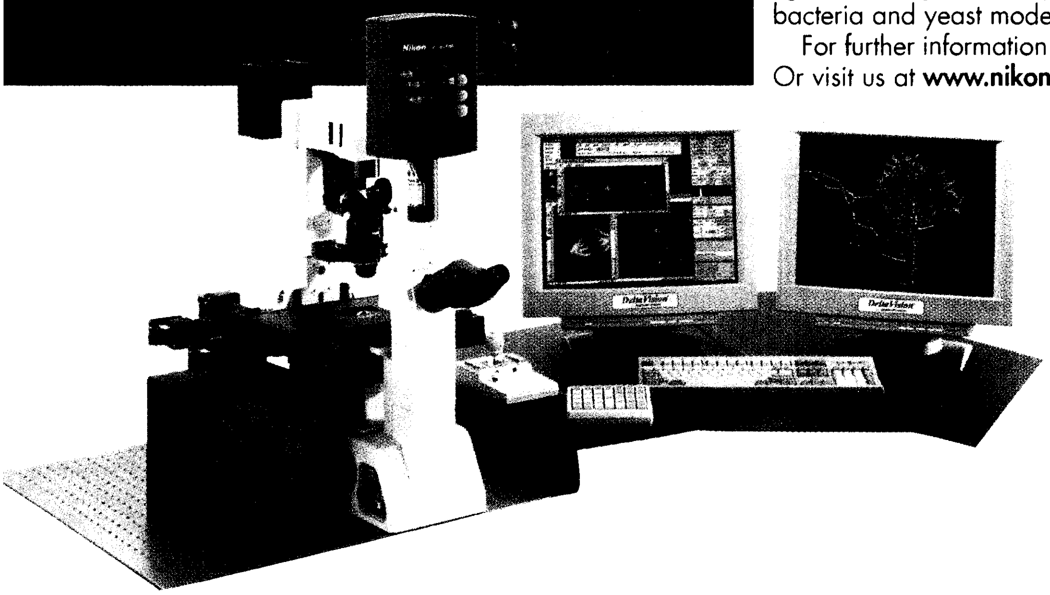

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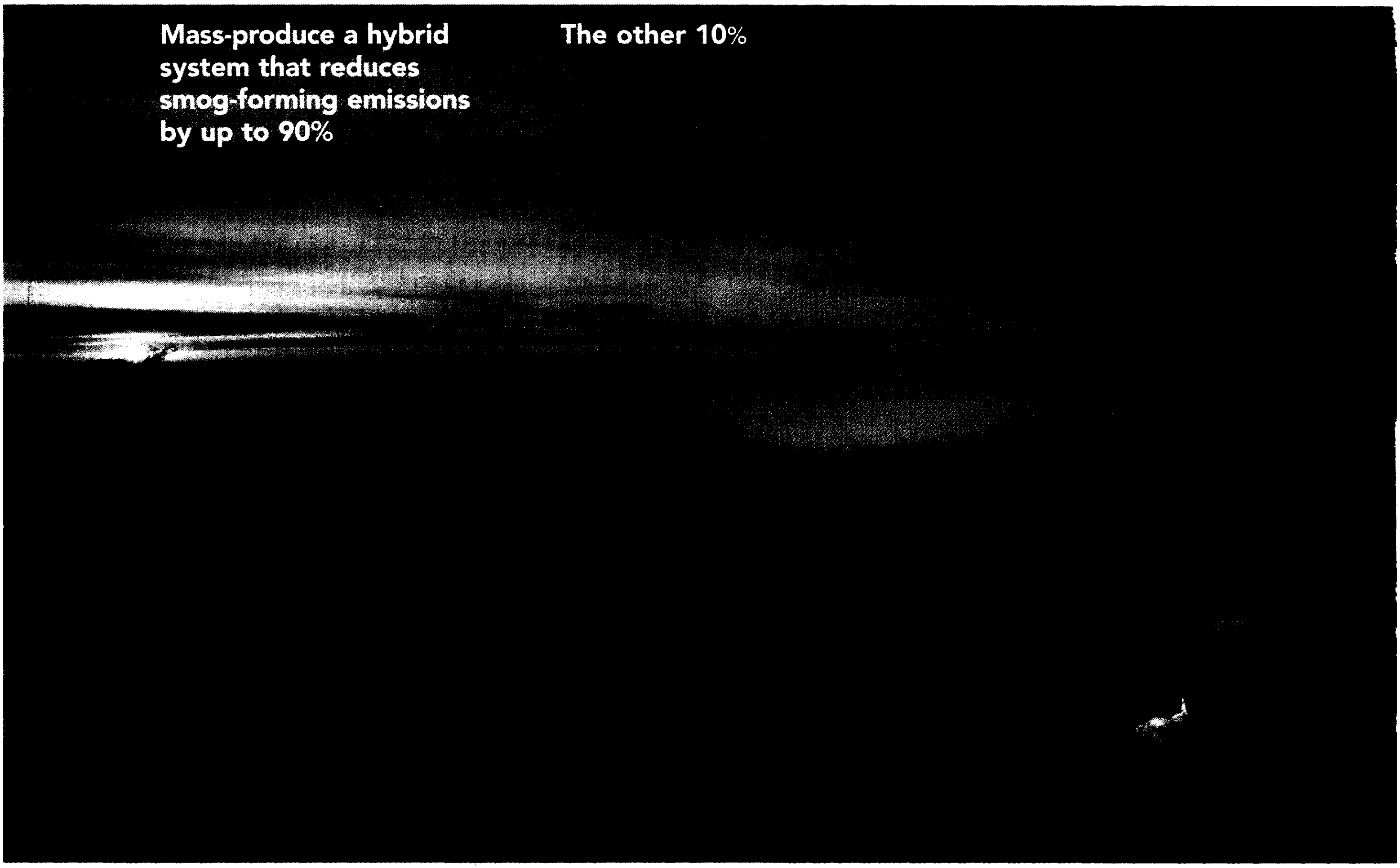

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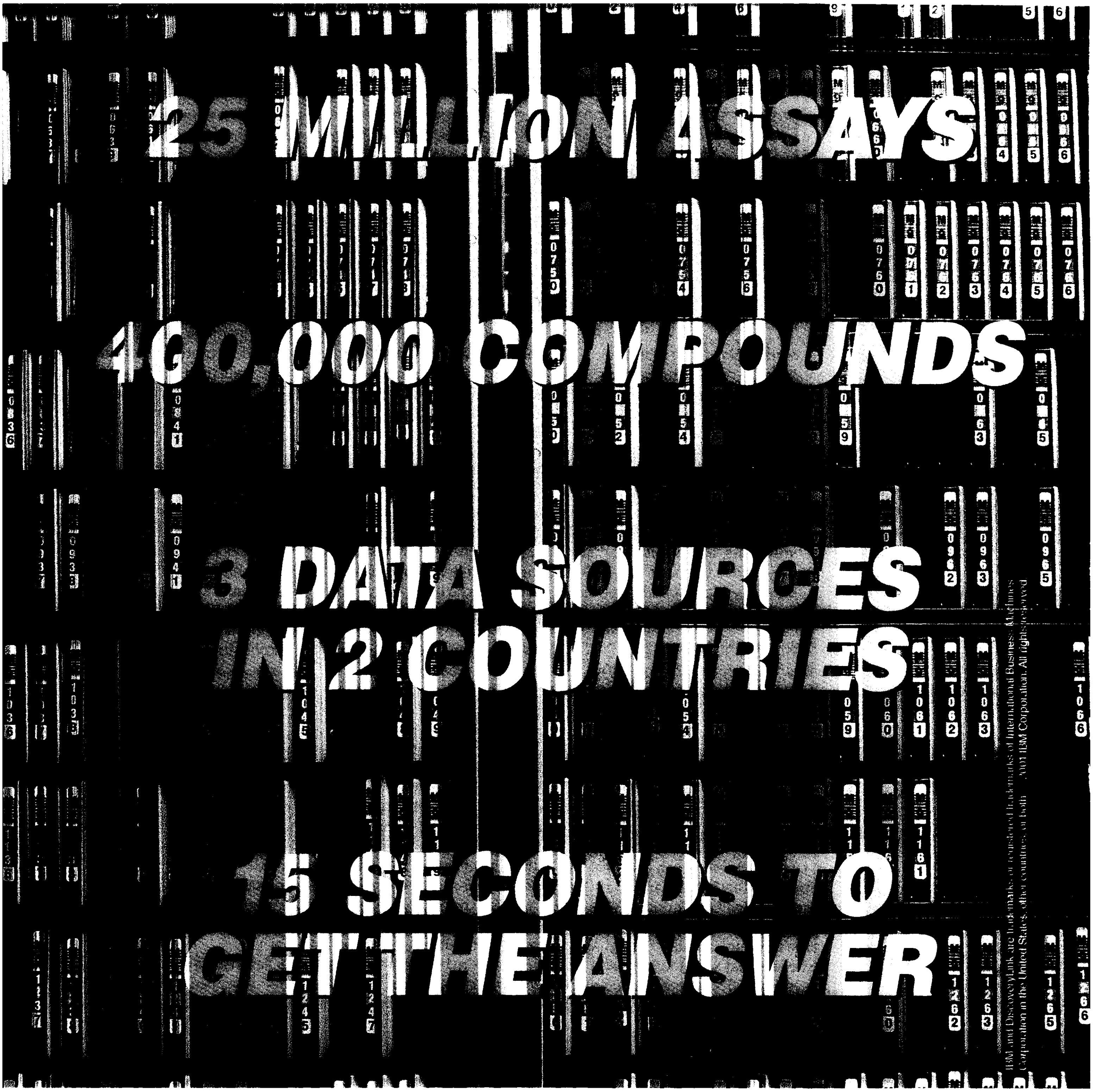

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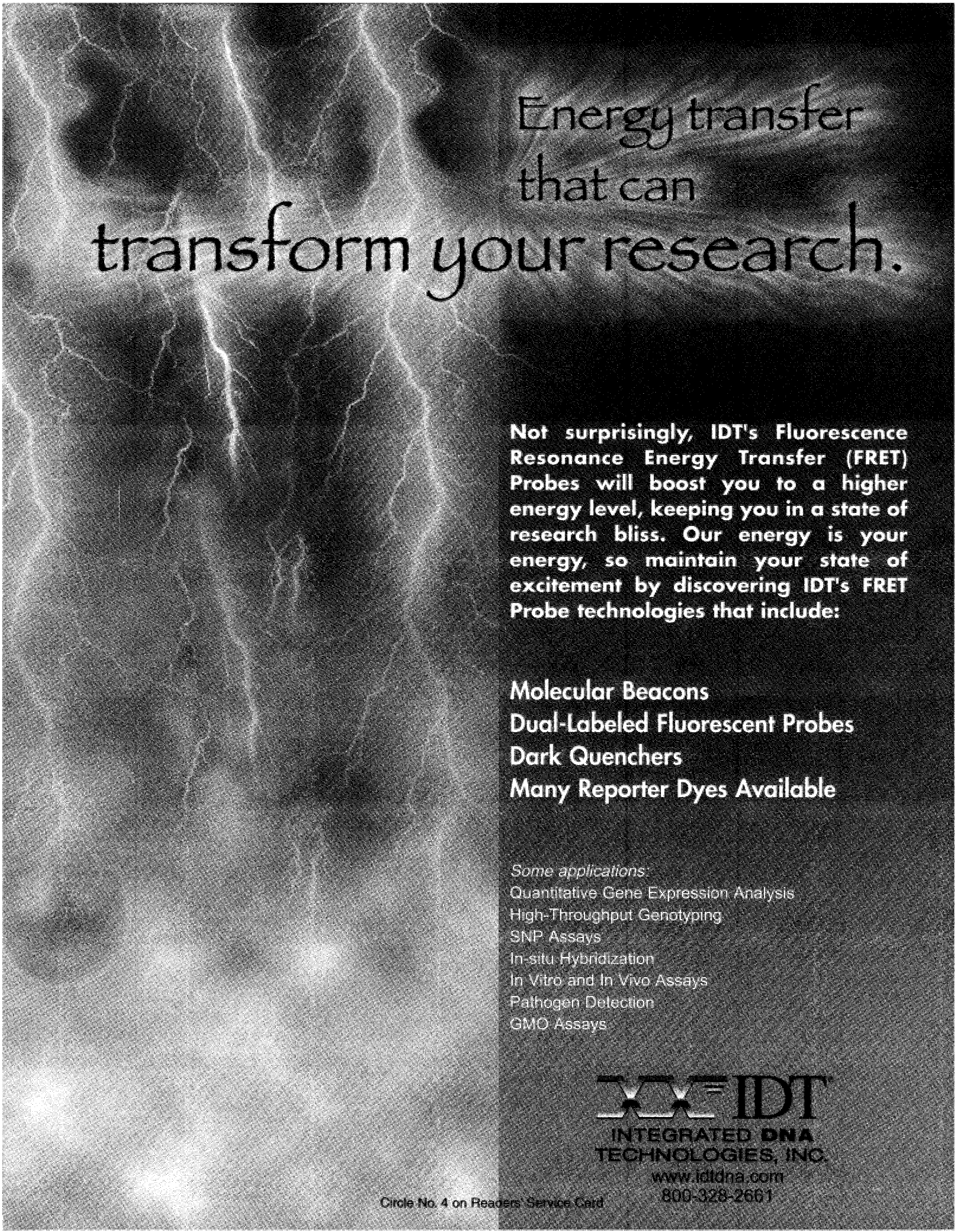
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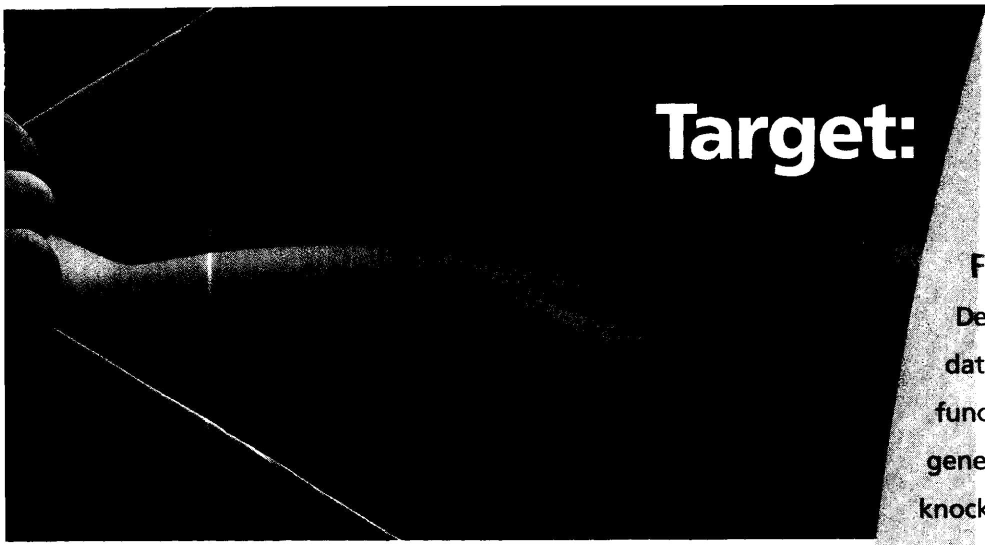

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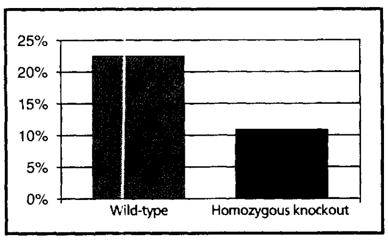
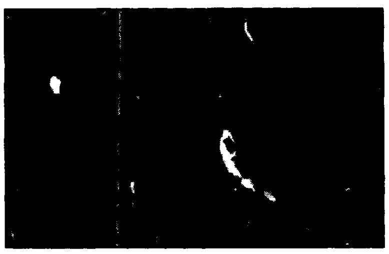
Phenotypic analysis
Gene: G protein-coupled receptor

Dual-energy x-ray absorptiometry was used to measure percent body fat in wild-type mice and homozygous knockout mice.

Percent body fat



Results indicate that percent body fat in homozygous mutants was significantly lower than that of the wild-type animals (11% vs 22.5%).



Histopathology reveals fat depletion in the brown adipose tissue of the knockout animals.

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Through a browser-enabled interface, DeltaBase subscribers can quickly review and compare phenotypic data, images and analysis summaries from genes belonging to gene families that have demonstrated a high degree of success as drug targets. This information can be used to identify valid targets and to support decisions about therapeutic value. In addition, animal models for all targets in DeltaBase are made available to subscribers for further study.

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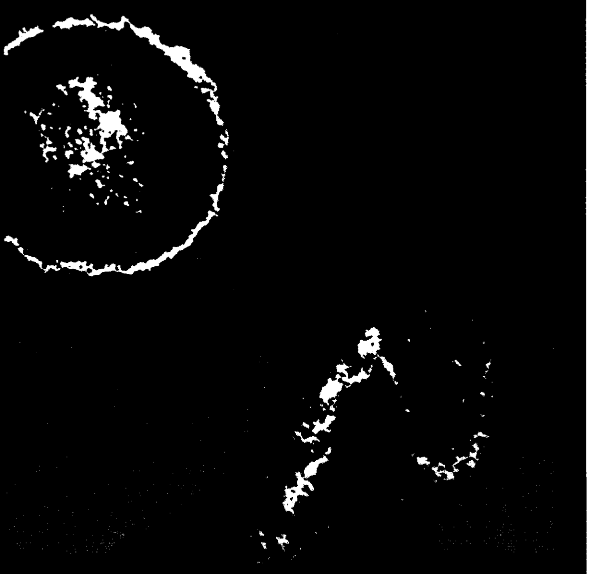

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