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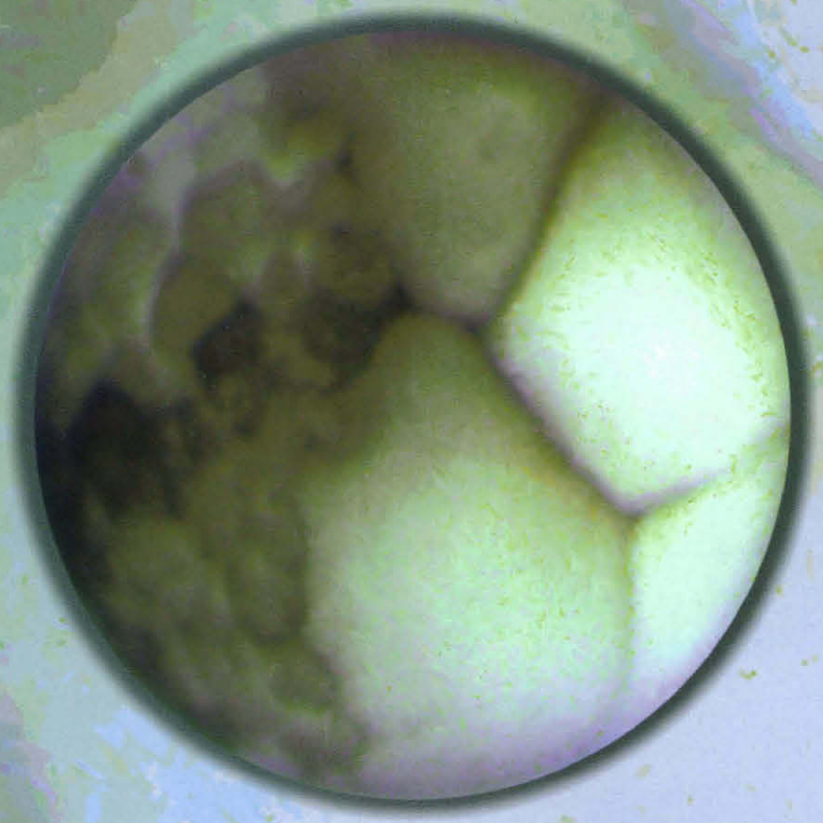

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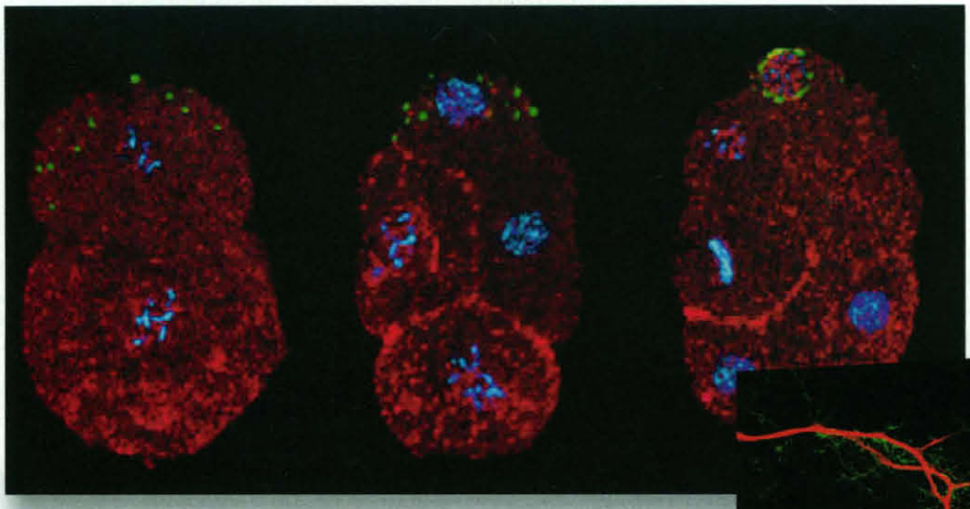

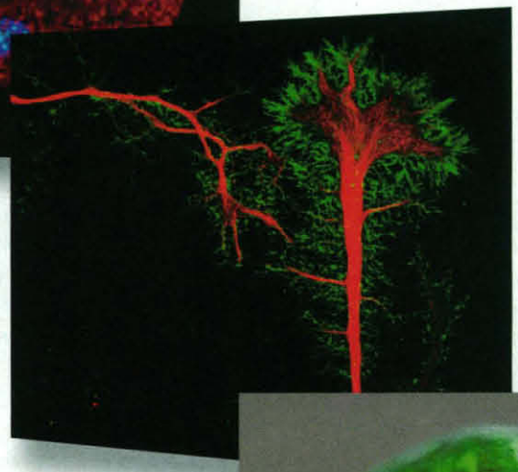

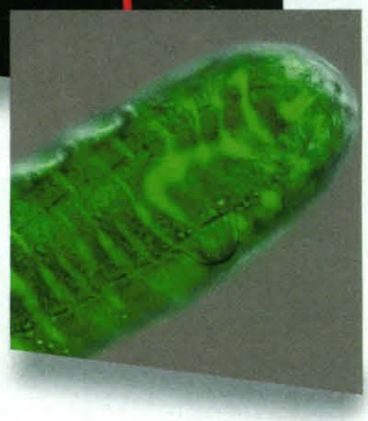

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Fig. 1 - Specimen: *C. elegans*; 3-photon excitation technique on Nikon Diaphot with 60X Plan Apo Oil objective. Provided by J. White, Univ. of Madison, WI and Bio-Rad.

Fig. 2 - Specimen: *Manduca sexta* pupa thoracic neurons; immunocytochemical technique on Nikon PCM2000 Confocal with 20X Plan Apo objective. Provided by P. Jansma, Univ. of Arizona.

Fig. 3 - Specimen: Drosophila embryos; time lapse GFP technique on Nikon TE300 with 10X Plan Fluor objective and simple PCI software. Provided by B. Burnip, Compix Inc. and B. Sanson, Univ. of Cambridge, UK.

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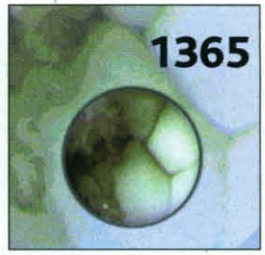

COVER This *Xenopus laevis* embryo (1 mm) demonstrates that expression of constitutively active p90 ribosomal S6 kinase is sufficient to induce metaphase arrest. Therefore, this kinase is the only substrate of the mitogen-activated protein kinase pathway required for cytostatic factor activity, which arrests the cell cycle of vertebrate eggs and embryos at metaphase. [Image: S. D. Gross]

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Top women scientists speak out

NEWS

NEWS OF THE WEEK

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RESEARCH

RESEARCH ARTICLE

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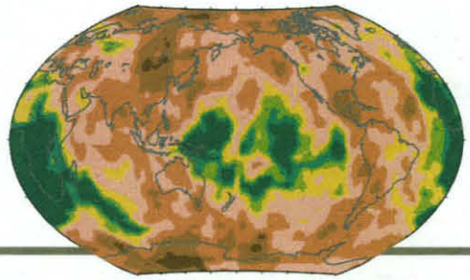

1326

Highs and lows of a deep mantle transition

TECHNICAL COMMENTS

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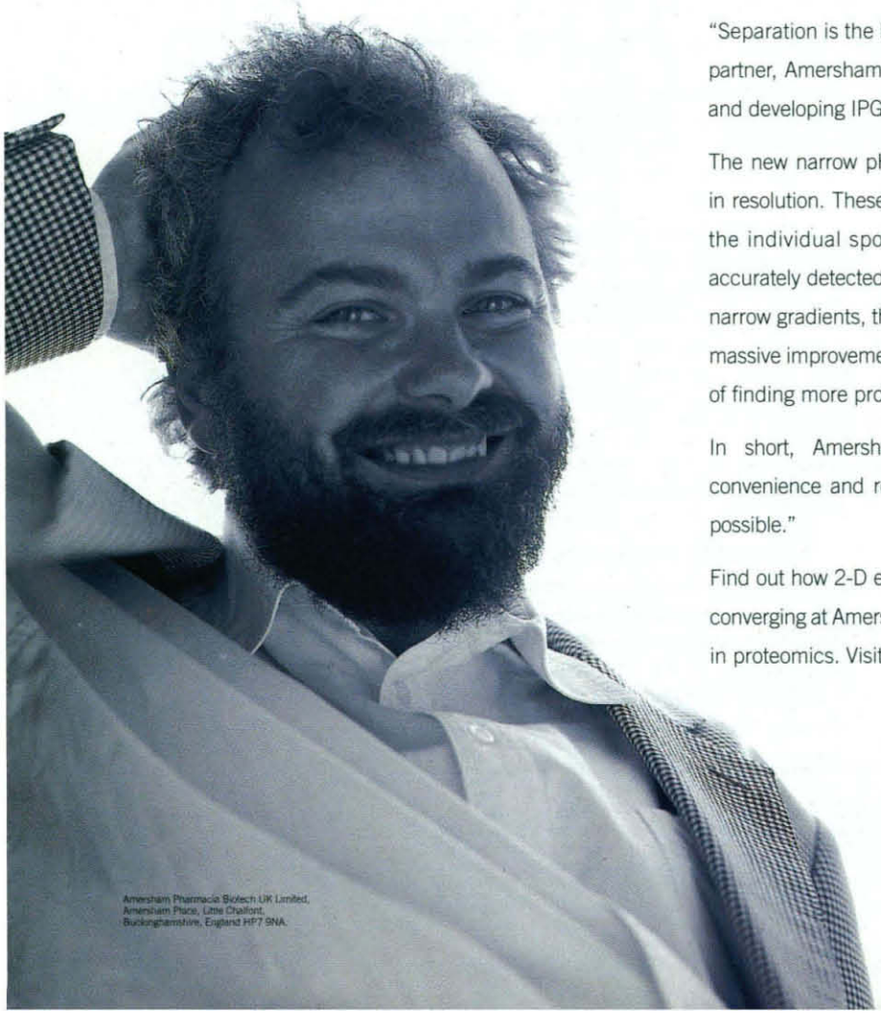

Dr. Hanno Langen, head of the proteomics group at Hoffmann-LaRoche genetics department.

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A SOLID-SOLID TRANSITION AT D"

Just above the outer liquid iron core lies a thin layer in the solid silicate mantle, called D", that is seismically anomalous. The nature of this important coupling layer between the core and the mantle remains poorly defined. Sidorin *et al.* (p. 1326) combined global tomographic models with waveform analysis of seismic phases that sample the D" layer to derive a consistent model for its structure. A solid-to-solid phase transition at about 200 kilometers above the core mantle boundary provides the most plausible explanation for the data they analyzed. They suggest that D" is a region that varies in elevation above the core and that represents the third major discontinuity. Additional experimental data will be needed to characterize the minerals involved in this proposed transition.

RAPID MELTING REVEALED

Melting of a solid normally involves nucleation of the liquid phase at defects or inclusions at its surface. However, if heated rapidly enough with sufficiently high energy, a semiconductor surface can melt completely and homogenously before thermal processes can begin to relax the process. Observing the loss of crystalline order directly requires extremely fast x-ray diffraction methods. Siders *et al.* (p. 1340; see the Perspective by Nelson) have now used picosecond x-ray pulses to observe such nonthermal melting in single-crystal films of germanium.

HIV MOVES IN

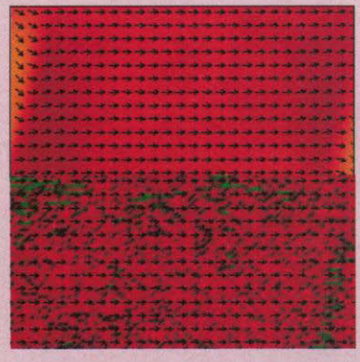
Two surprising pieces of information concerning the early events in human immunodeficiency virus–type 1 infection have been obtained by Zhang *et al.* (p. 1353) from an animal model of heterosexual viral transmission. They found that lymphocytes, rather than macrophages or dendritic cells, were the first cells infected when the virus was inoculated intravaginally. Furthermore, many of the infected cells were quiescent rather than actively dividing, as evidenced by the absence of early molecular markers of proliferation. Infected resting cells could still be found in lymph node biopsies of human patients after treatment with antiretroviral therapy. Understanding the state of this infected cell population is important to efforts directed at eradication of the virus from cellular reservoirs.

SAUROPOD VARIATION

Several newly identified Cretaceous-aged sauropod dinosaurs from the Sahara are reported by Sereno *et al.* (p. 1342). As a group, these sauropods, which range in age from 130 to 100 million years ago, seem to be relatively primitive compared to those on other continents. These data and comparison with other sauropods imply that the rate of skeletal evolution among these large dinosaurs was quite uneven.

EFFECTIVE EVEN ON THE FRINGE

Magnetic tunnel junctions can provide "nonvolatile" dynamic memory elements that remain in their on or off state even when power is lost. In spin-dependent magnetic tunnel junctions, which consist of a magnetically hard



reference layer and a switchable magnetically soft layer, magnetization in the hard reference layer decays with increasing switching cycles, despite the magnetic fields being considerably smaller than those required to switch the entire hard layer. McCartney *et al.* (p. 1337), using a magnetic imaging technique, identified large fringing magnetic fields that developed at the domain walls of the magnetically soft layer as the source of the decay of the magnetization. This finding should allow for the design of better magnetic memories.

MAKING THE TAG

The targeted degradation of proteins has emerged as an important regulatory mechanism in a variety of cellular processes. Proteolysis is initiated by covalent tagging of the protein with ubiquitin, which is the signal recognized by the degradation machinery. The enzymes that catalyze the addition of ubiquitin are known as ubiquitin-protein ligases; one of these, E6AP, mediates the degradation of the tumor suppressor p53 in most cervical carcinomas. Huang *et al.* (p. 1321) describe the crystal structure of the catalytic domain of E6AP alone and in complex with the ubiquitin-conjugating enzyme that serves to provide activated ubiquitin to the ligase.

MITOCHONDRIA IN ACTION

Intracellular calcium stores play a crucial role in the function of excitable cells. An important part of this calcium storage system are the mitochondria, which provide the cell with energy. Jonas *et al.* (p. 1347) have demonstrated in vivo a physiological link between excitation of the cell membrane and mitochondrial electrical activity. They succeeded in recording signals from mitochondria in intact presynaptic boutons of the squid giant synapse. After neuronal stimulation, they saw a calcium-dependent increase in mitochondrial ion channel activity.

PINPOINTING RSKS

During development, some neurons undergo cell death if they are deprived of growth factors. Signals that contribute to such growth factor–dependent survival are mediated, at least in part, by activation of mitogen-activated protein kinases (MAPKs), but the crucial target of the MAPKs has been unknown. Bonni *et al.* (p. 1358) report that the protein kinase Rsk2 (a member of the pp90 ribosomal protein S6 kinase family), which is phosphorylated and activated by MAPKs, may mediate the effects on cell survival in cerebellar granule neurons exposed to brain-derived neurotrophic factor. Rsk 2 appears to have two ways of influencing cell survival: It phosphorylates and thus suppresses the effects of BAD, a protein that promotes apoptosis. Rsk2 also phosphorylates and activates the transcription factor CREB (cAMP response element binding protein). Activation of CREB may in turn enhance expression of Bcl2, a protein that promotes cell survival. In a Perspective, Nebreda and Gavin discuss these findings and those from a pair of reports that define another role of Rsks in the control of the cell cycle. Before fertilization, most vertebrate eggs are at metaphase of meiosis II. Cytostatic factor (CSF) is the name given to an enzymatic activity present in

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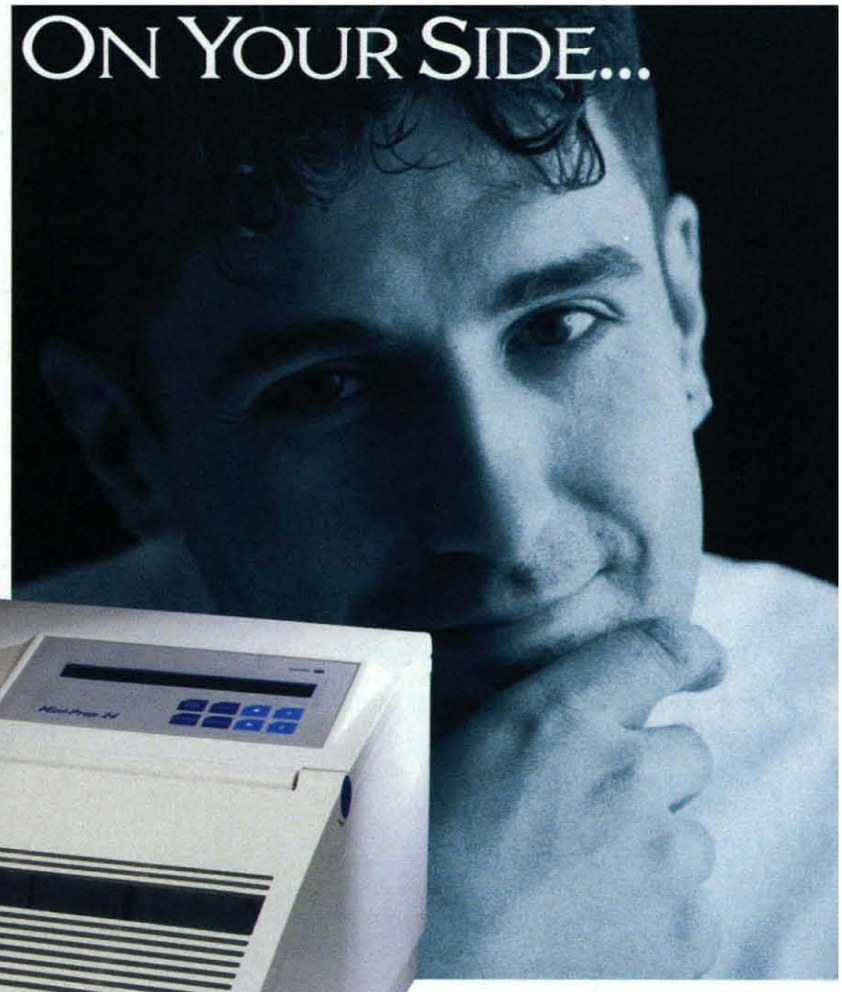

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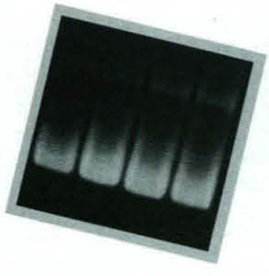

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such eggs, which, when injected into dividing embryos, causes mitotic arrest in metaphase. Such "CSF arrest" can be initiated by the protein kinase Mos, which activates the sequential activation of MAPK kinase MEK and the p42 MAPK. The critical target of p42 MAPK has now been identified as the protein kinase p90 Rsk. Bhatt and Ferrell (p. 1362) show that depletion of Rsk from *Xenopus* egg extracts prevents mitotic arrest in response to activated Mos. Gross *et al.* (p. 1365; see the cover) demonstrate that activation of Rsk requires its phosphorylation by p42 MAPK and the 3-phosphatidylinositol–dependent kinase–1 (PDK-1). They also constructed a constitutively active form of Rsk that caused metaphase arrest when infected into blastomeres of two-cell *Xenopus* embryos. Activation of Rsk is thus necessary and sufficient to cause CSF arrest.

WAKE ME WHEN YOU NEED ME

Regulatory proteins have generally been thought of as constitutively active. Puigserver *et al.* (p. 1368) now show that coactivators are actually inactive if they are not associated with their complementary DNA-binding proteins. Once a transcription factor and its coactivator unite, a conformational change in the coactivator occurs that leads to recruitment of additional coactivators such as the histone acetyltransferases SRC-1 and p300/CBP. Hence, transcription factor docking provides a specificity mechanism.

REMEMBER THOSE SHOTS?

Vaccination enables an immune response to be mounted quickly upon exposure to the pathogen. This accelerated response is a result of a "memory" being established in the appropriate lymphocytes. It has been thought that T cell memory persistence requires the T cell's antigen receptor to either see antigen or at least major histocompatibility complex (MHC) proteins. Swain *et al.* (p. 1381) studied the memory requirements of CD4 T cells, and Murali-Krishna *et al.* (p. 1377) studied those of CD8 T cells. Neither subset requires MHC proteins or antigen to be maintained. An understanding of what generates such memory and how it is maintained will lay the groundwork for the development of more efficacious vaccination strategies (see the news story by Hagmann).

TECHNICAL COMMENT SUMMARIES

BACE2, a Homolog of BACE, in the Down Syndrome Region of Chromosome 21

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full//286/5443/1255a

Vassar *et al.* (Research Articles, 22 October, p. 735) identified and characterized BACE, a transmembrane aspartyl protease with β-secretase activity that cleaves the amyloid precursor protein (APP). One of the products released is the 39– to 43–amino acid amyloid β peptide (Aβ), a key component of the brain plaques that are the hallmark of Alzheimer's disease (AD). The identification of an AD-specific β-secretase may lead to the development of inhibitors of this protease to treat this disease.

Saunders *et al.* now extend this work by determining the chromosomal localization of BACE. They identified four expressed sequence tags (AI290317, AF150387, R55298, and H60581) that are identical in amino acid sequence to BACE. R55298 has been previously mapped to chromosome 11q23.2–11q23.3, and the investigators mapped H60581 to centimorgan position 121.037 on the summary map for chromosome 11. Separately, Fan *et al.* also localized BACE to chromosome 11q23.3 by radiation hybrid analyses.

Saunders *et al.* searched the Genbank database and retrieved the sequence for complementary DNAs (AF050171, AF117892) that encode a BACE homolog (BACE2) located on chromosome 21q22.3. BACE and BACE2 exhibit 52% amino acid sequence identity and 68% similarity. BACE2 contains two aspartyl protease active sites at similar positions to those in BACE, which suggests that BACE2 is also a putative β-secretase. In response, Fan *et al.* report that experiments using BACE antisense oligonucleotides in HEK 293 cells suggest that BACE2 is unlikely to be the principal β-secretase, at least not in these cells.

Of added interest, BACE2 maps to the obligatory Down syndrome (DS; trisomy 21) region. Thus, in addition to the contribution of an additional copy of the APP gene in DS patients, the chromosomal localization of BACE2 suggests that enhanced β-secretase activity may also contribute to the elevated generation of Aβ and its abundant deposition in the brains of middle-aged DS patients.

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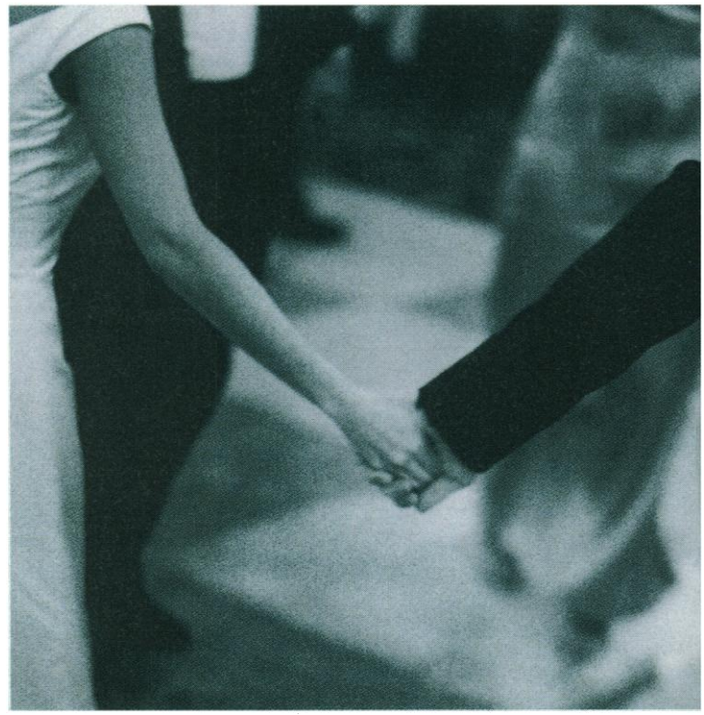

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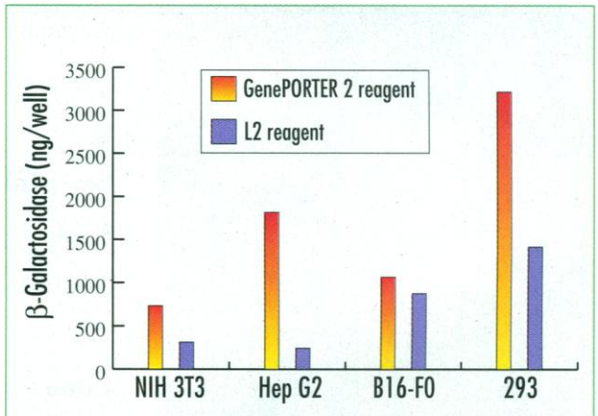

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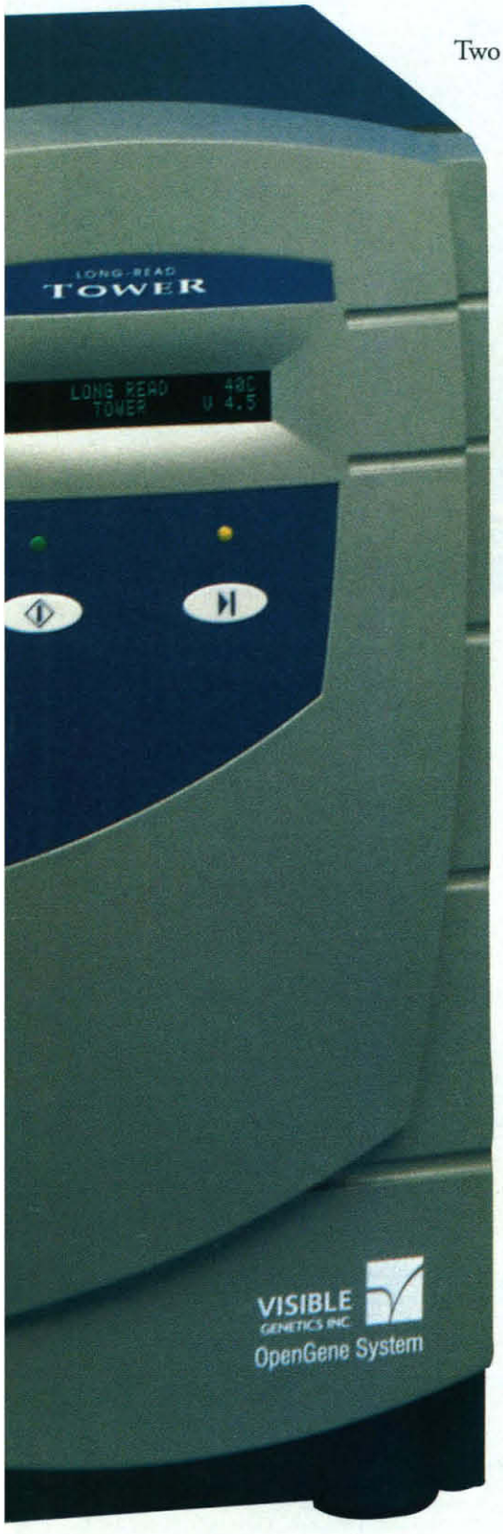

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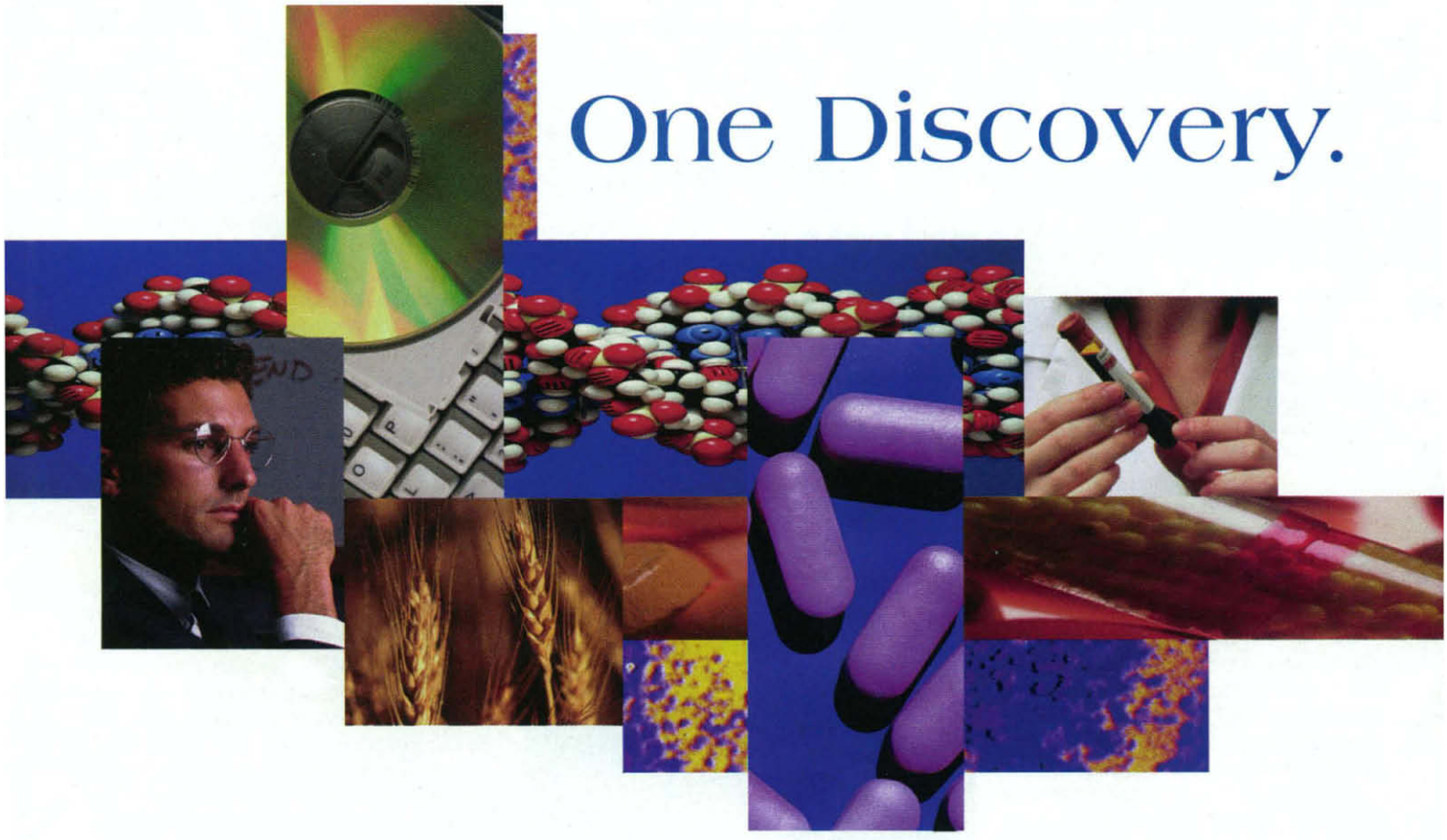

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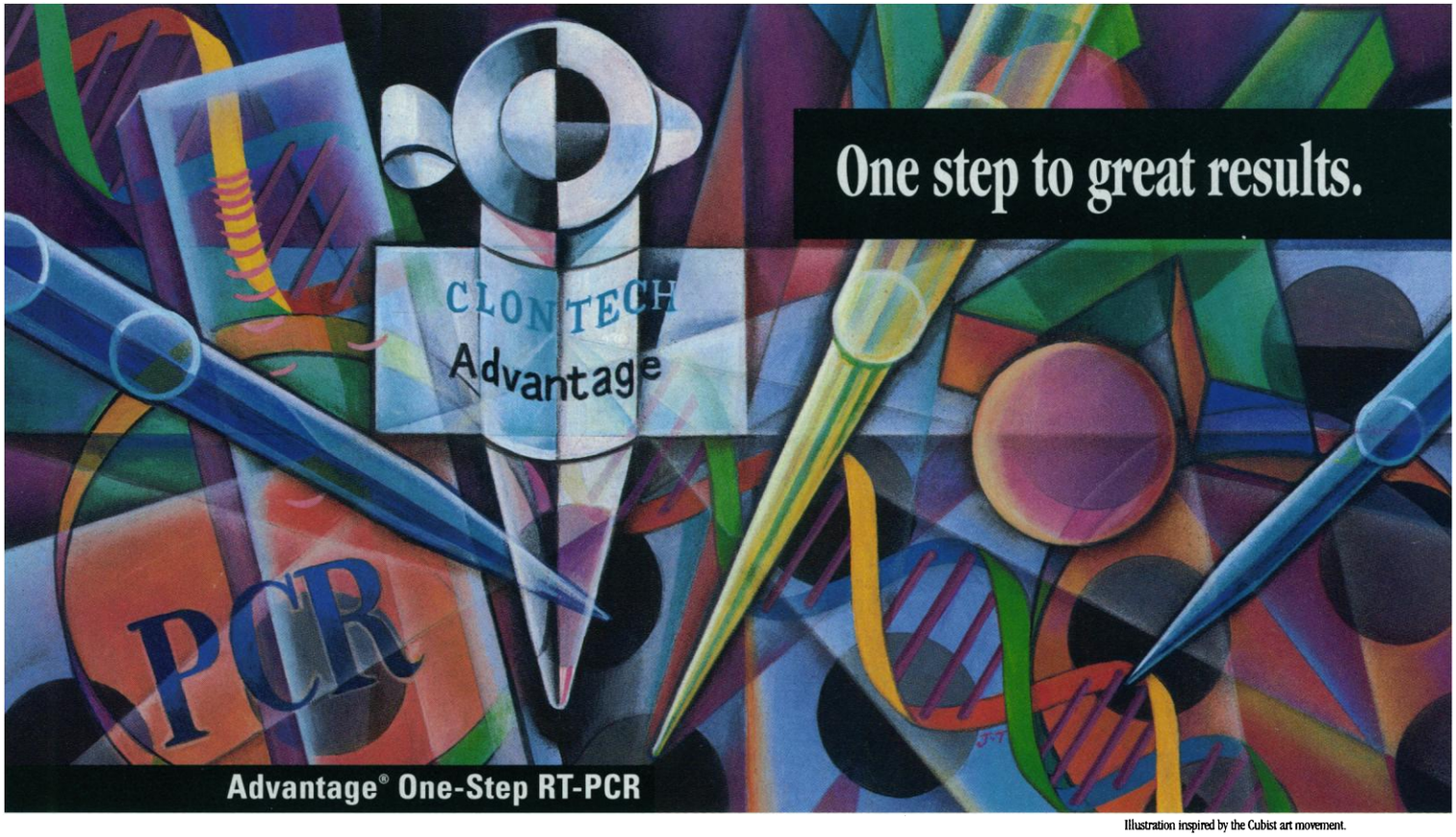

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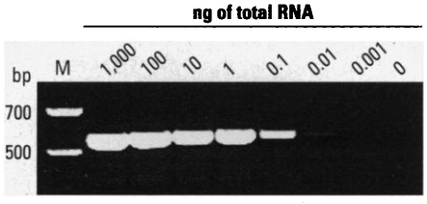

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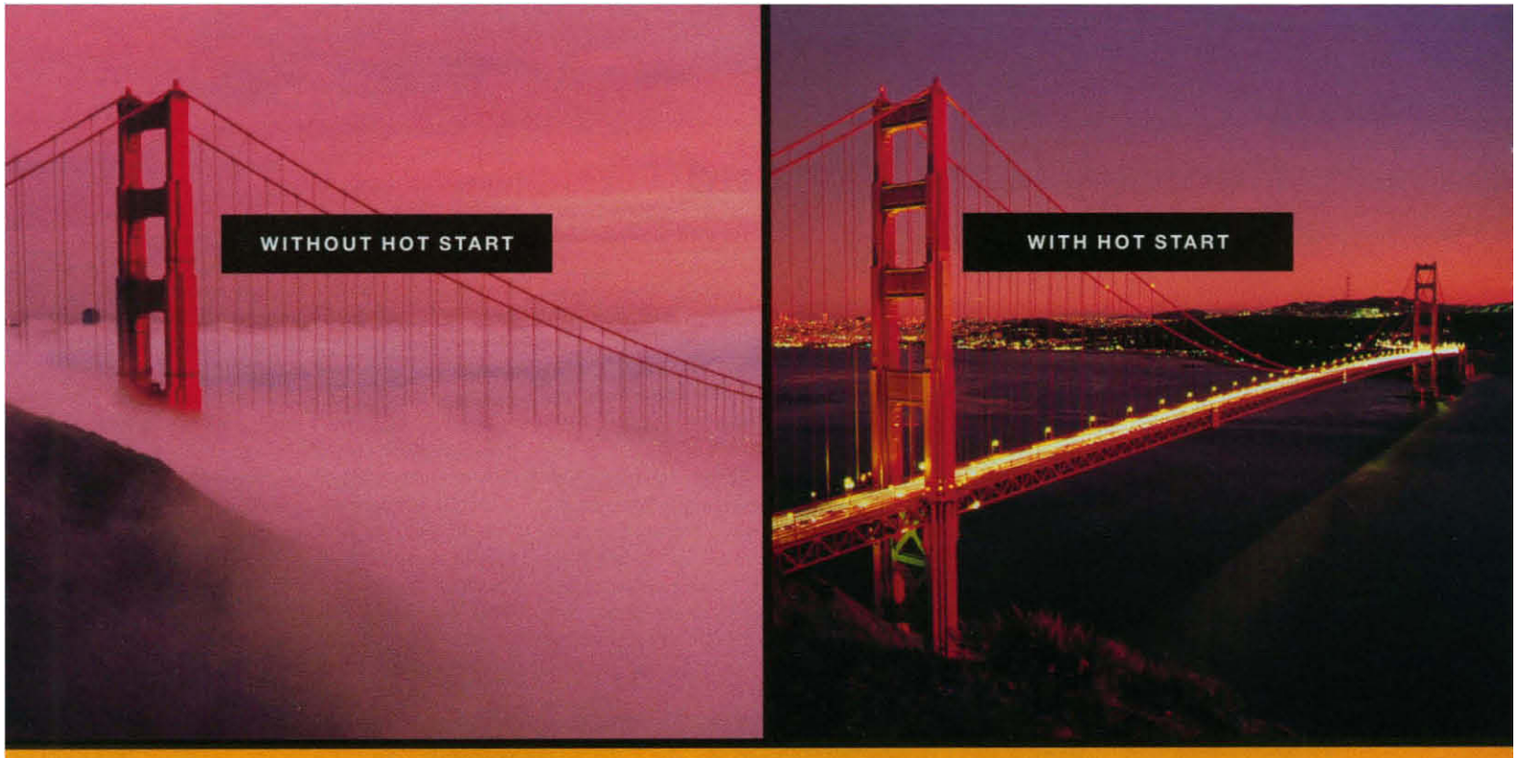

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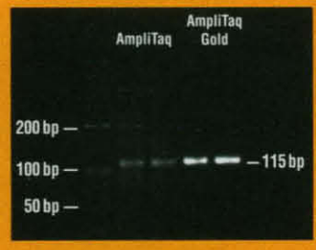

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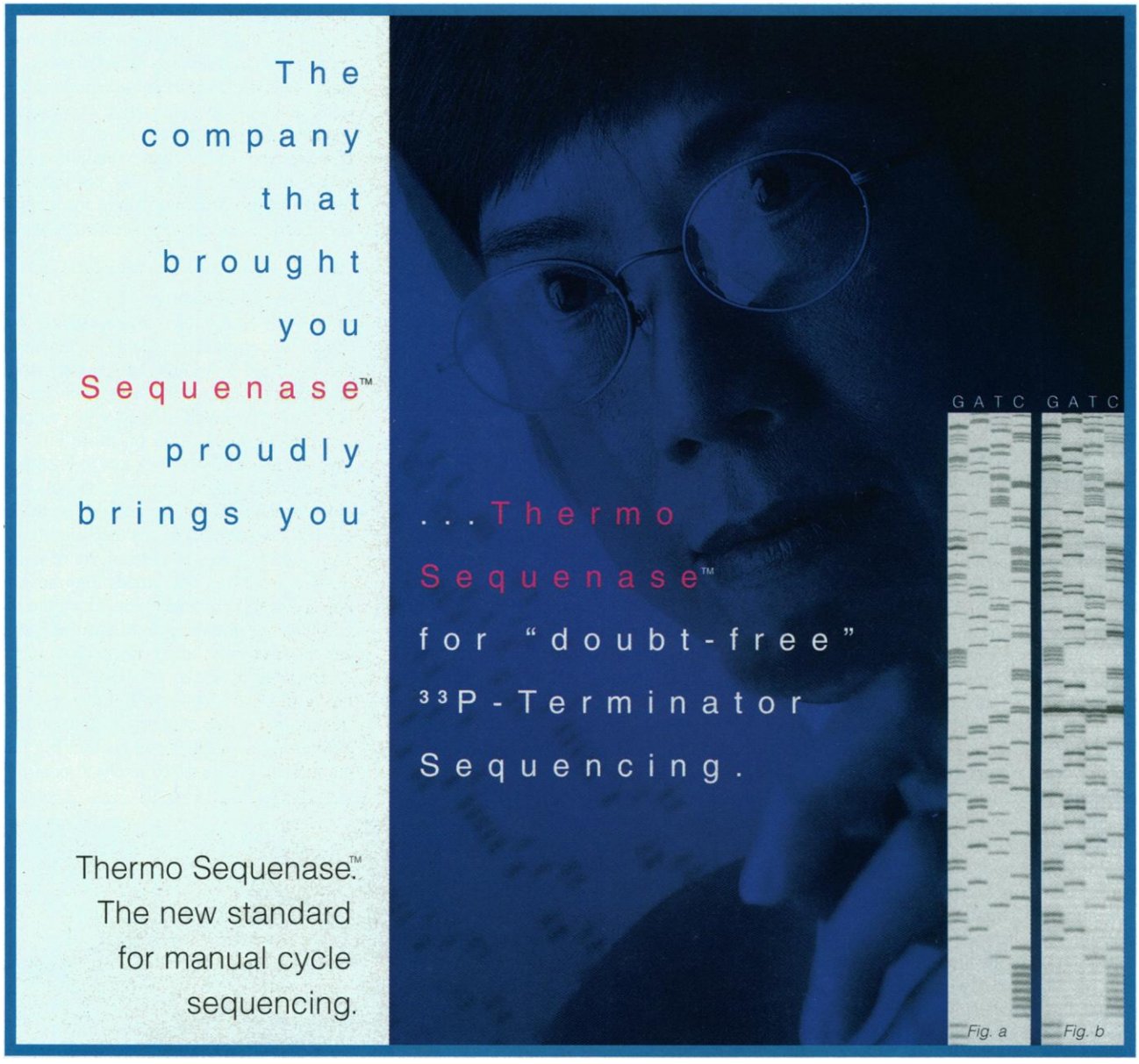

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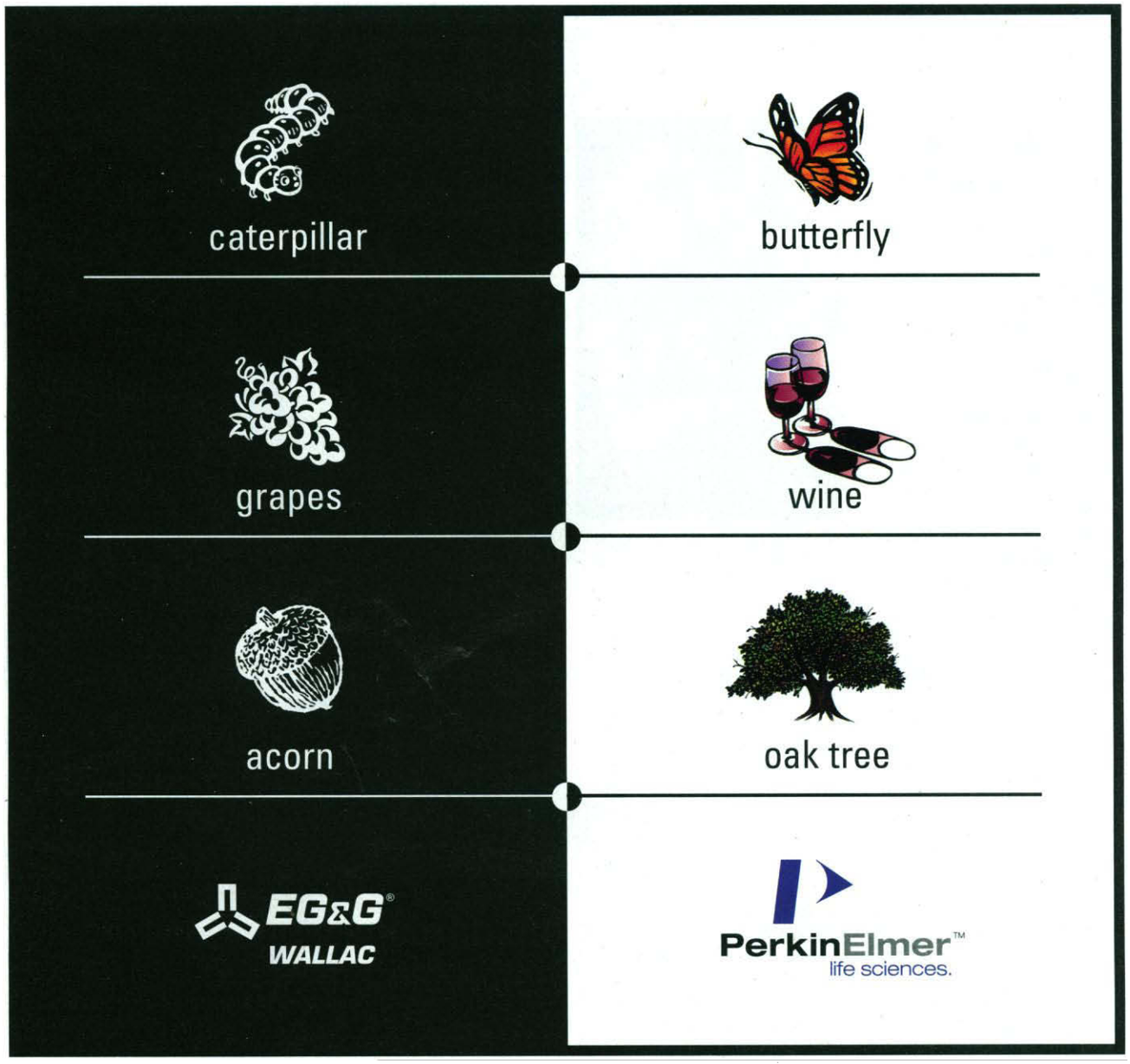

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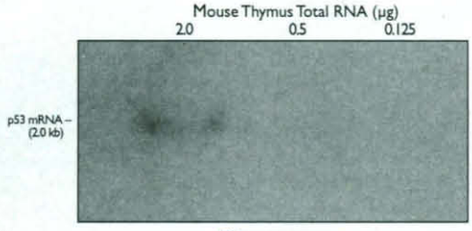
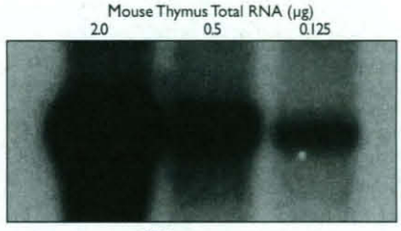


40 hr exposure

Your Northern with ULTRAhyb™



40 hr exposure

Duplicate Northern blots were prepared using mouse thymus total RNA and hybridized with a DNA probe to p53 at a concentration of 1×10^6 cpm probe/ml hybridization solution. Incubation and washing conditions were as per protocol for each solution. Both hybridizations were incubated overnight. Blots were exposed to film for 40 hours.

1. *Molecular Cloning: A Laboratory Manual*, 1989. Sambrook, J. Fritsch, E.F., Maniatis, T. Cold Spring Harbor Laboratory Press.

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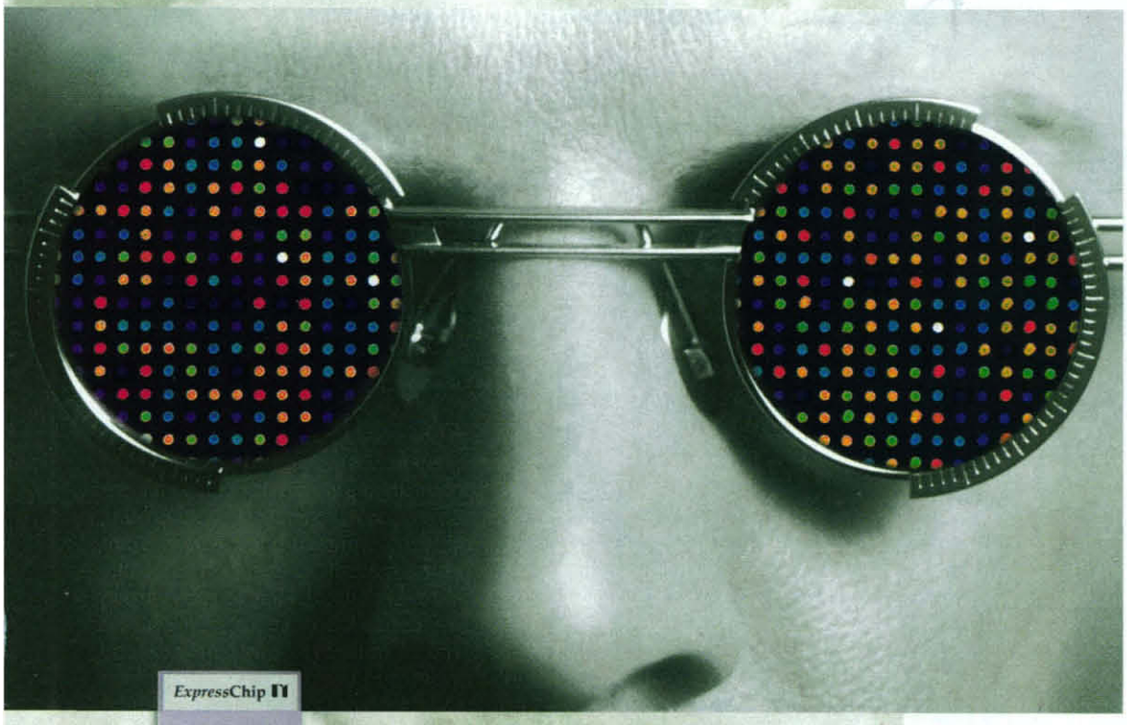

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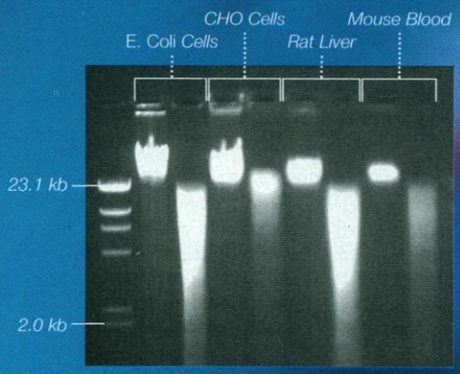

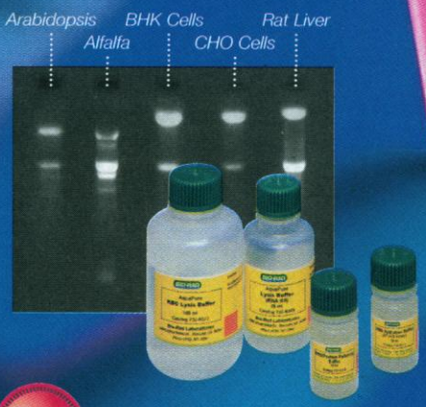

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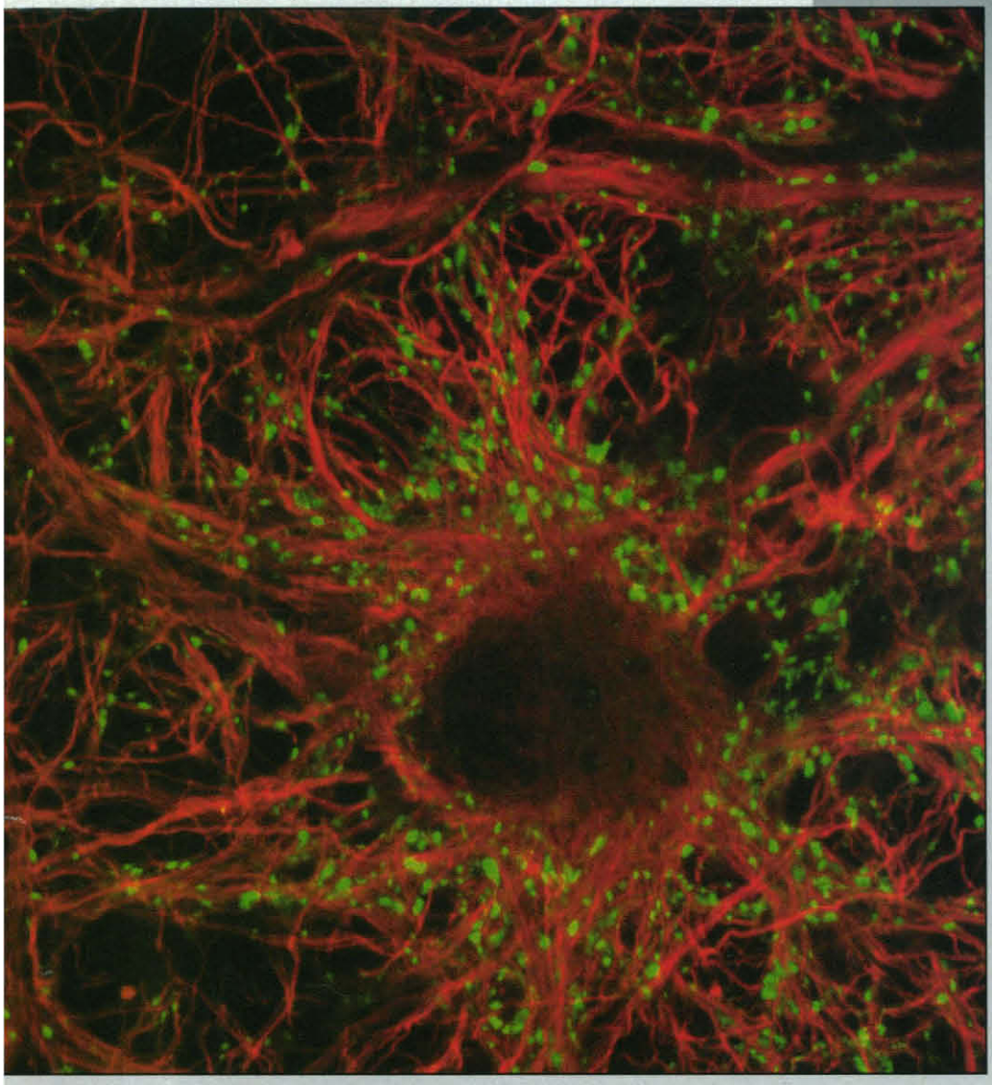

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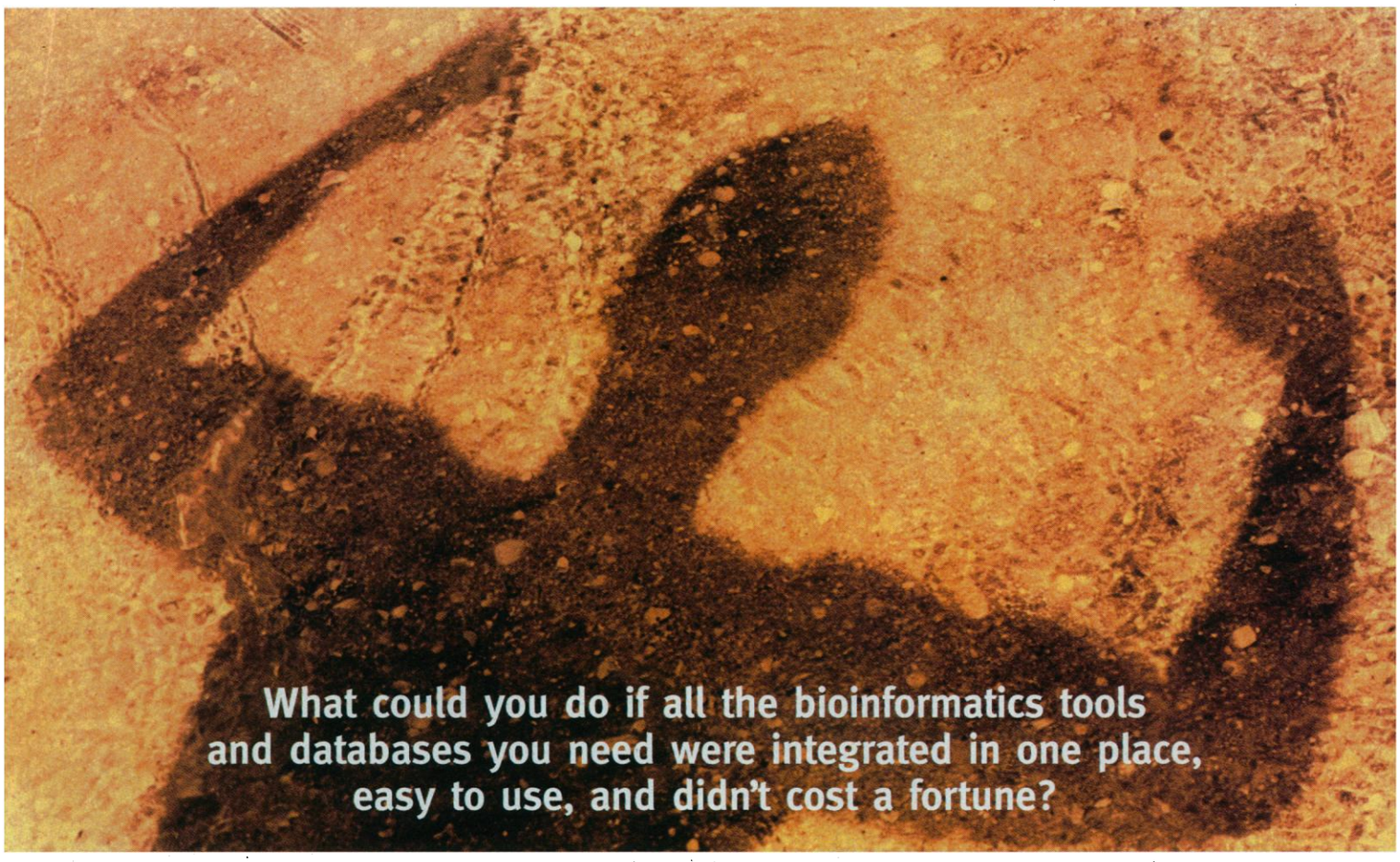

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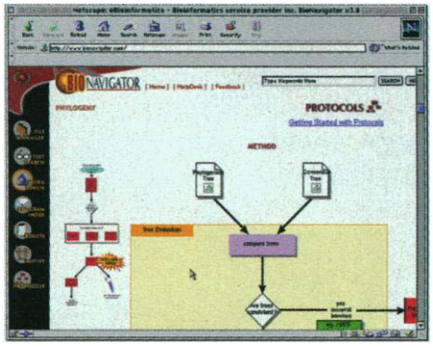

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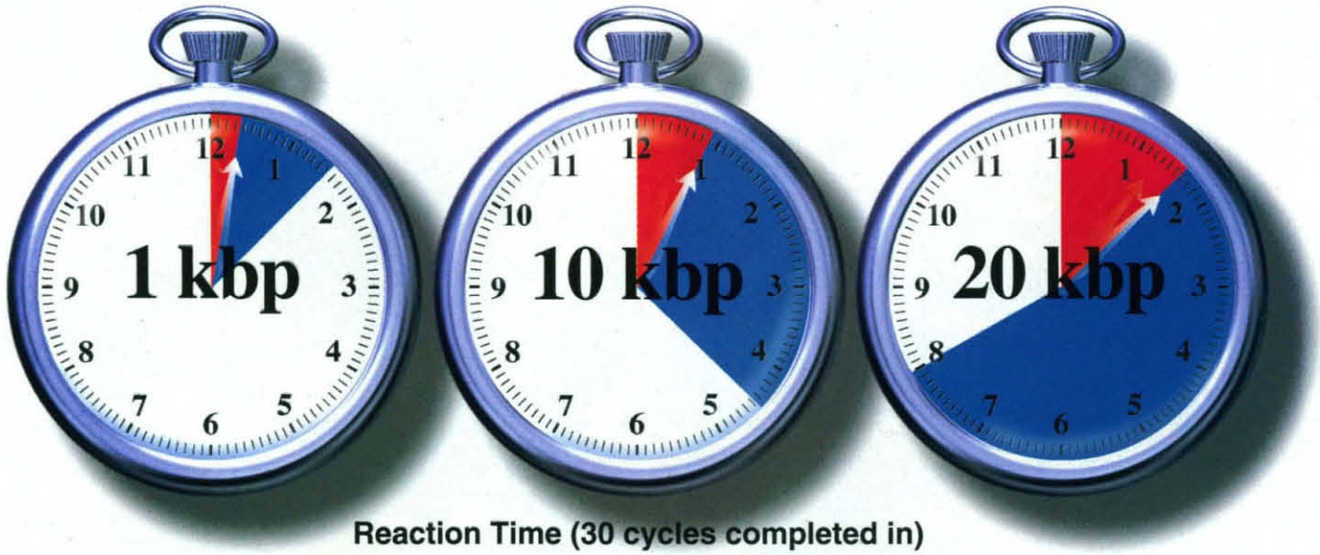

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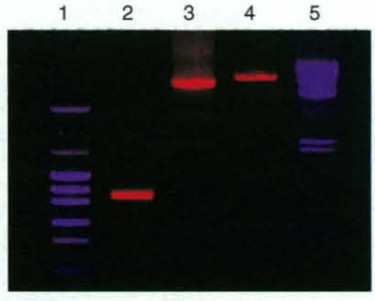

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2. 1 kbp
3. 10 kbp
4. 20 kbp
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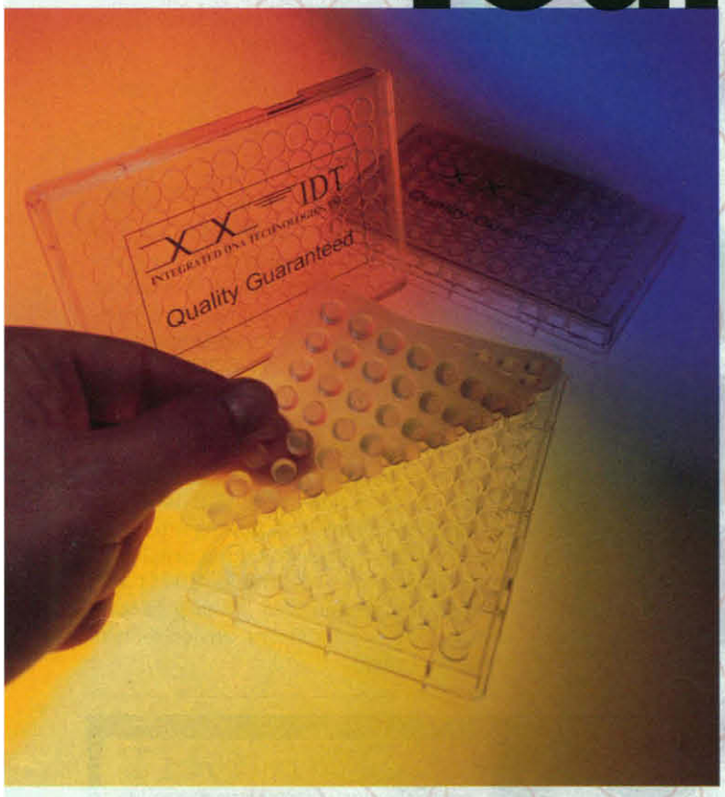

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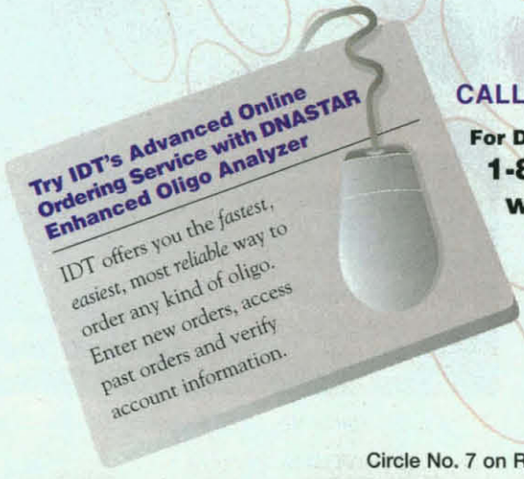

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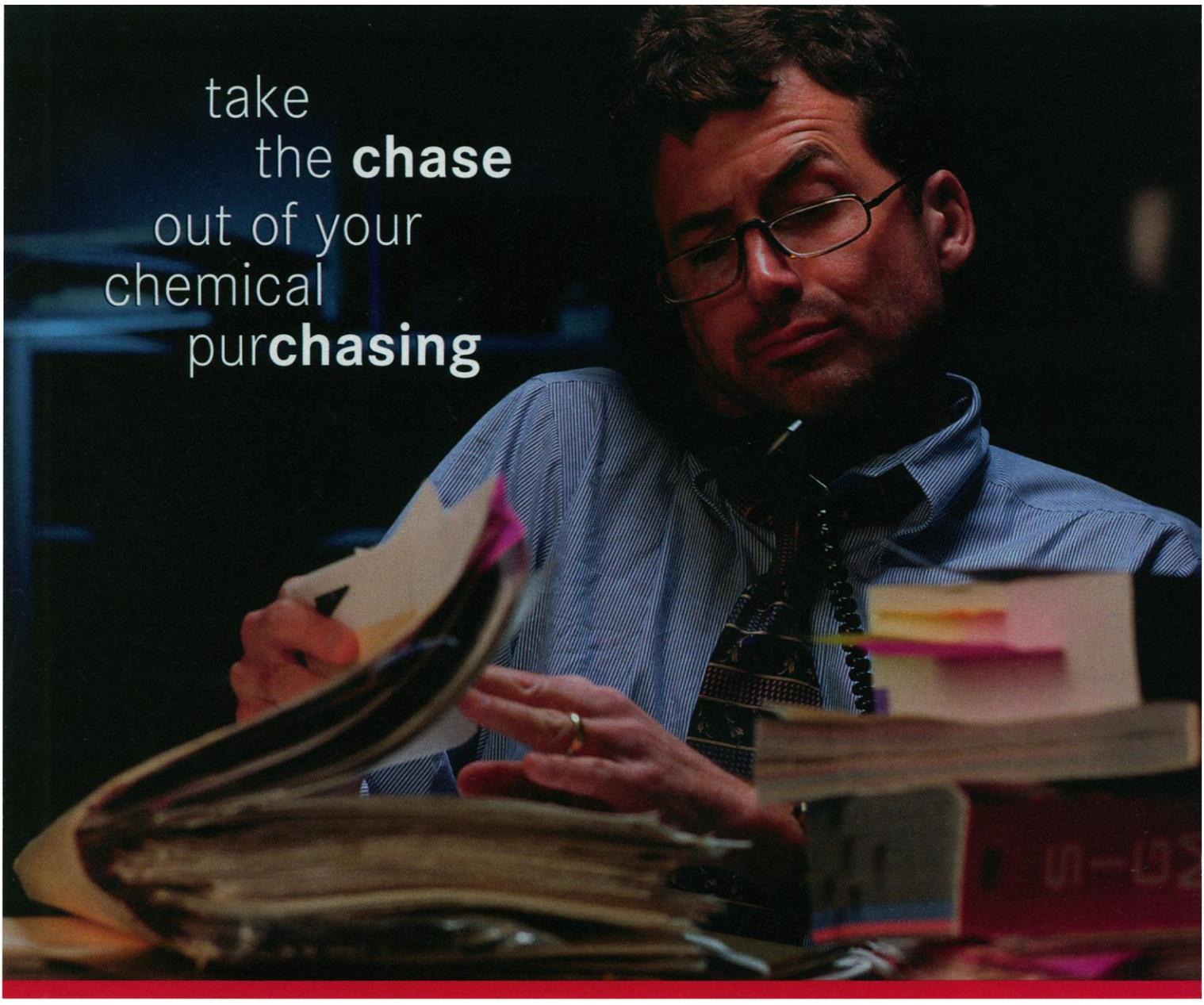

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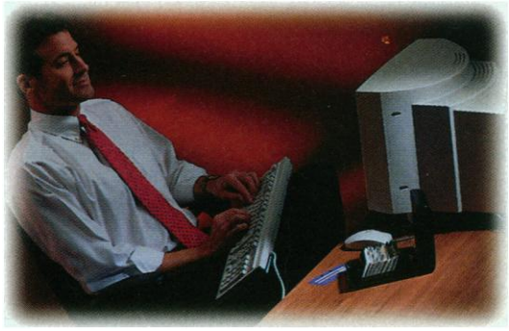

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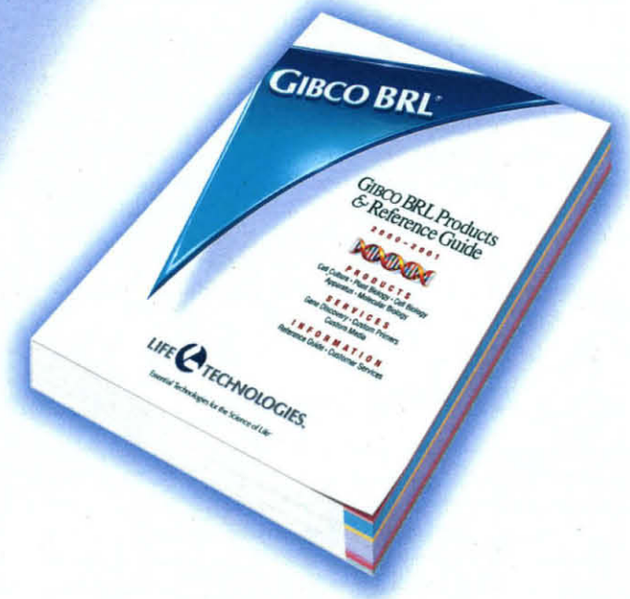

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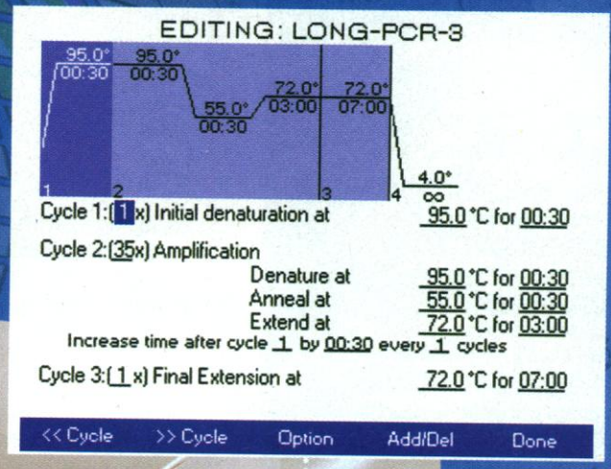

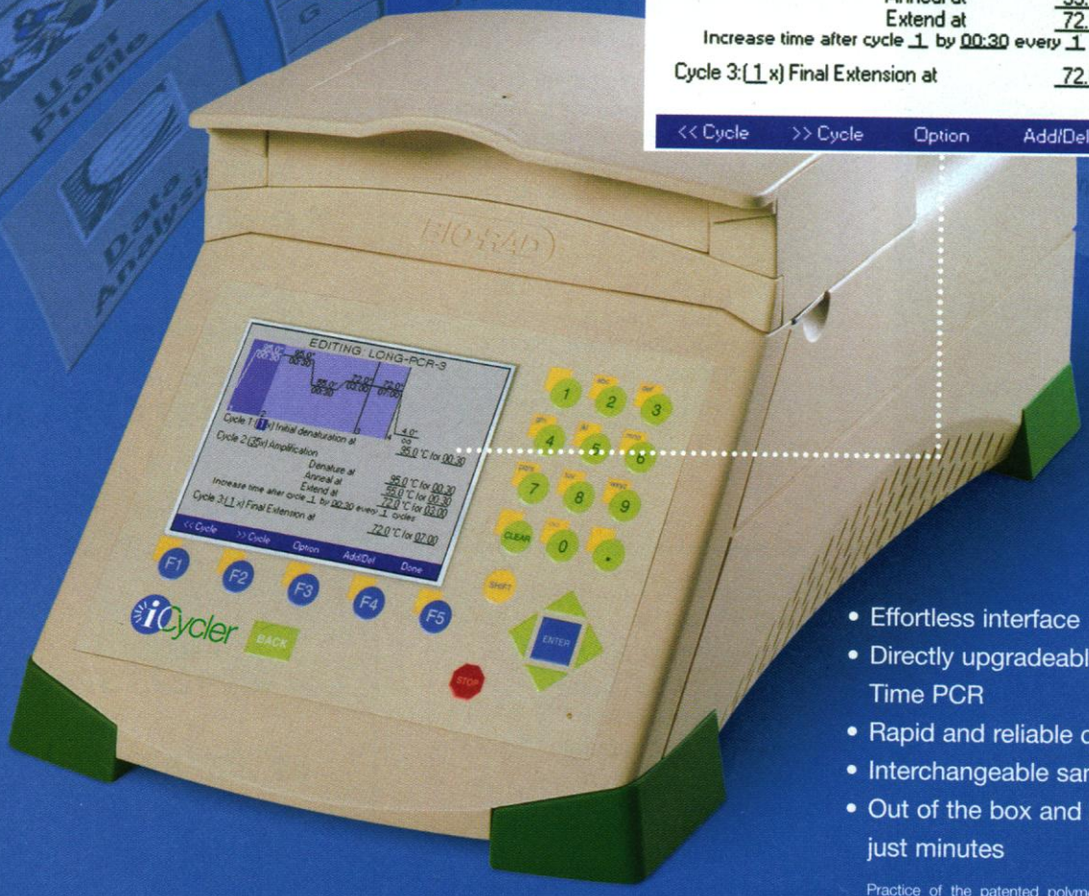

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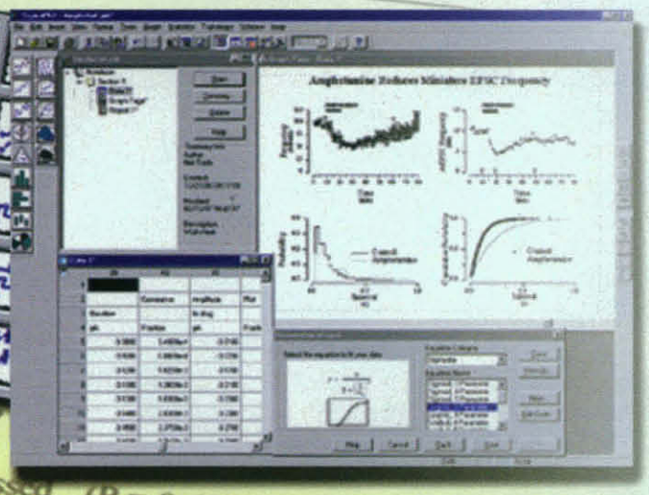

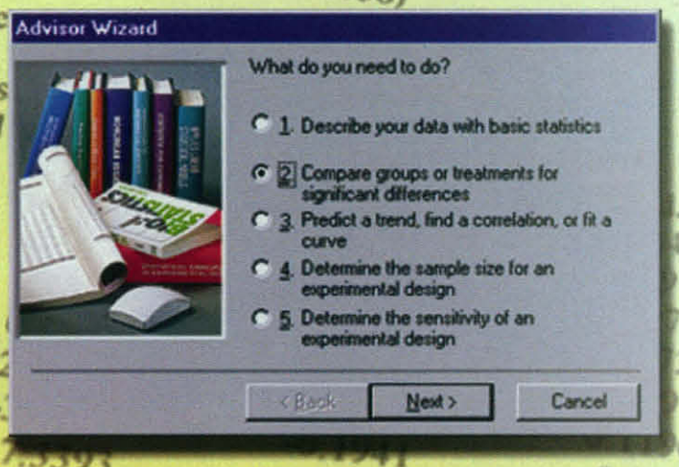

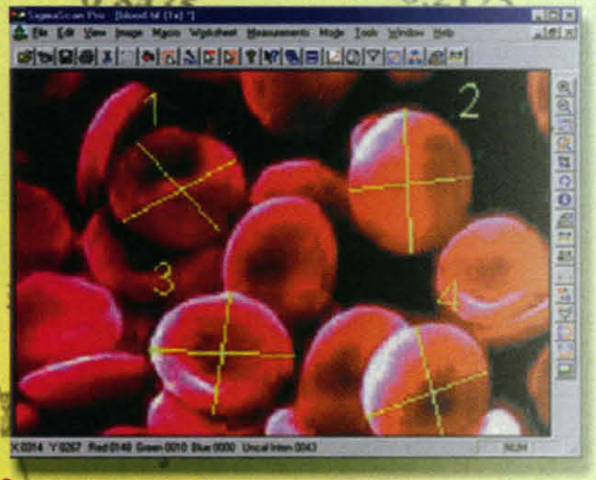

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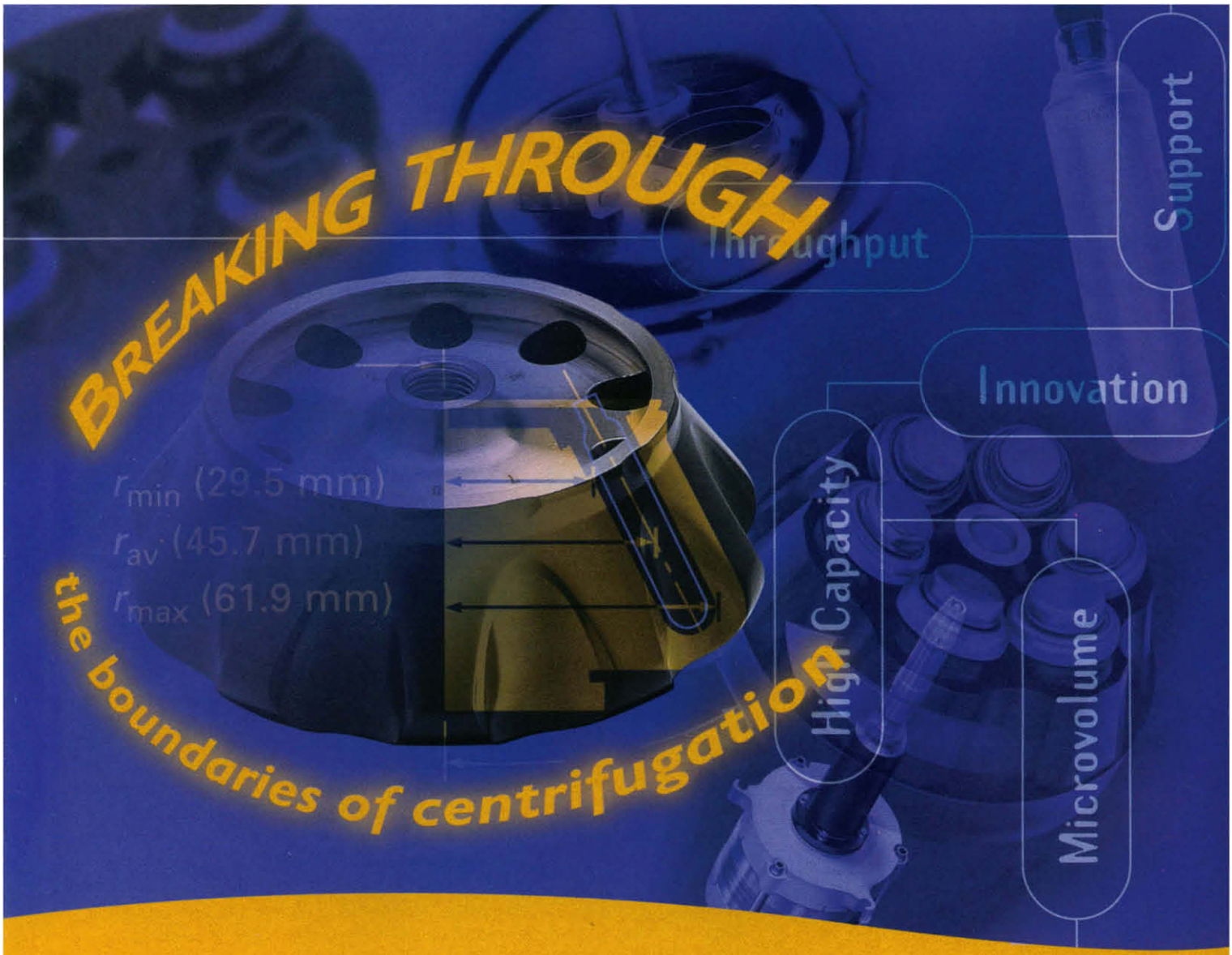

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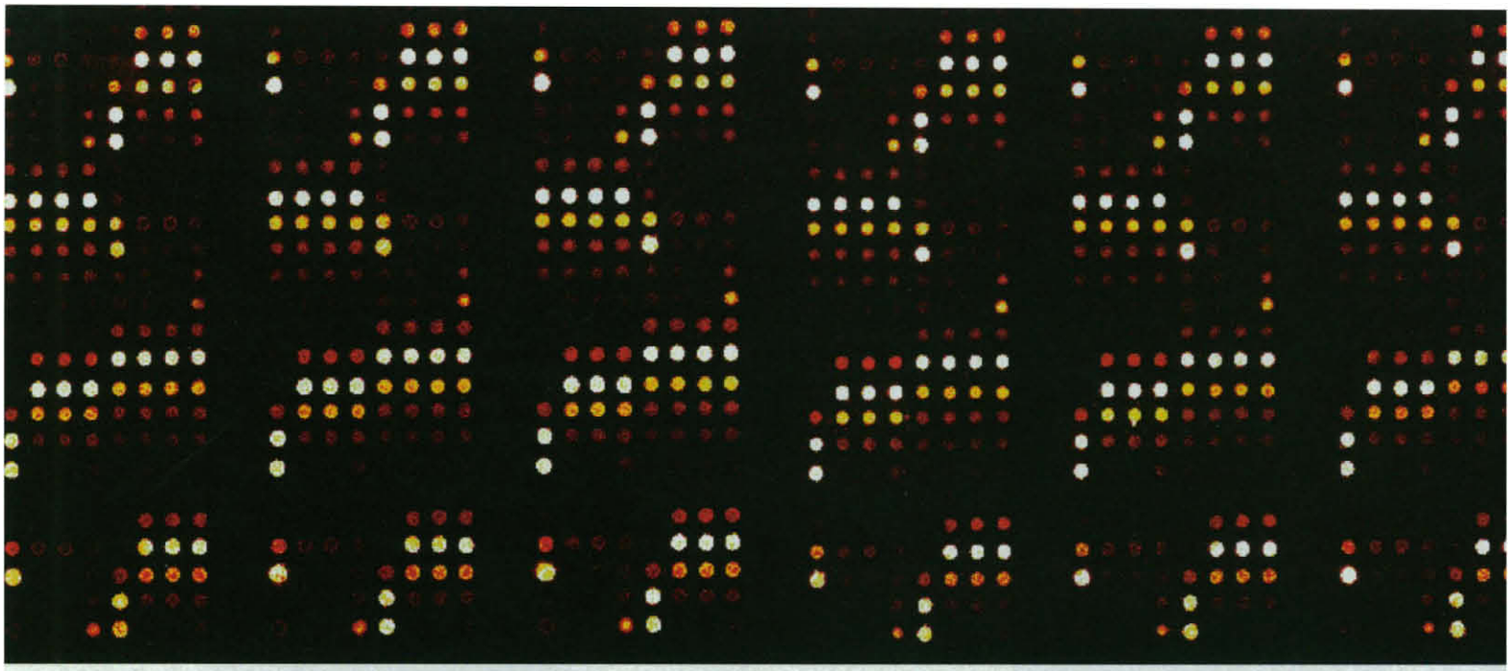

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