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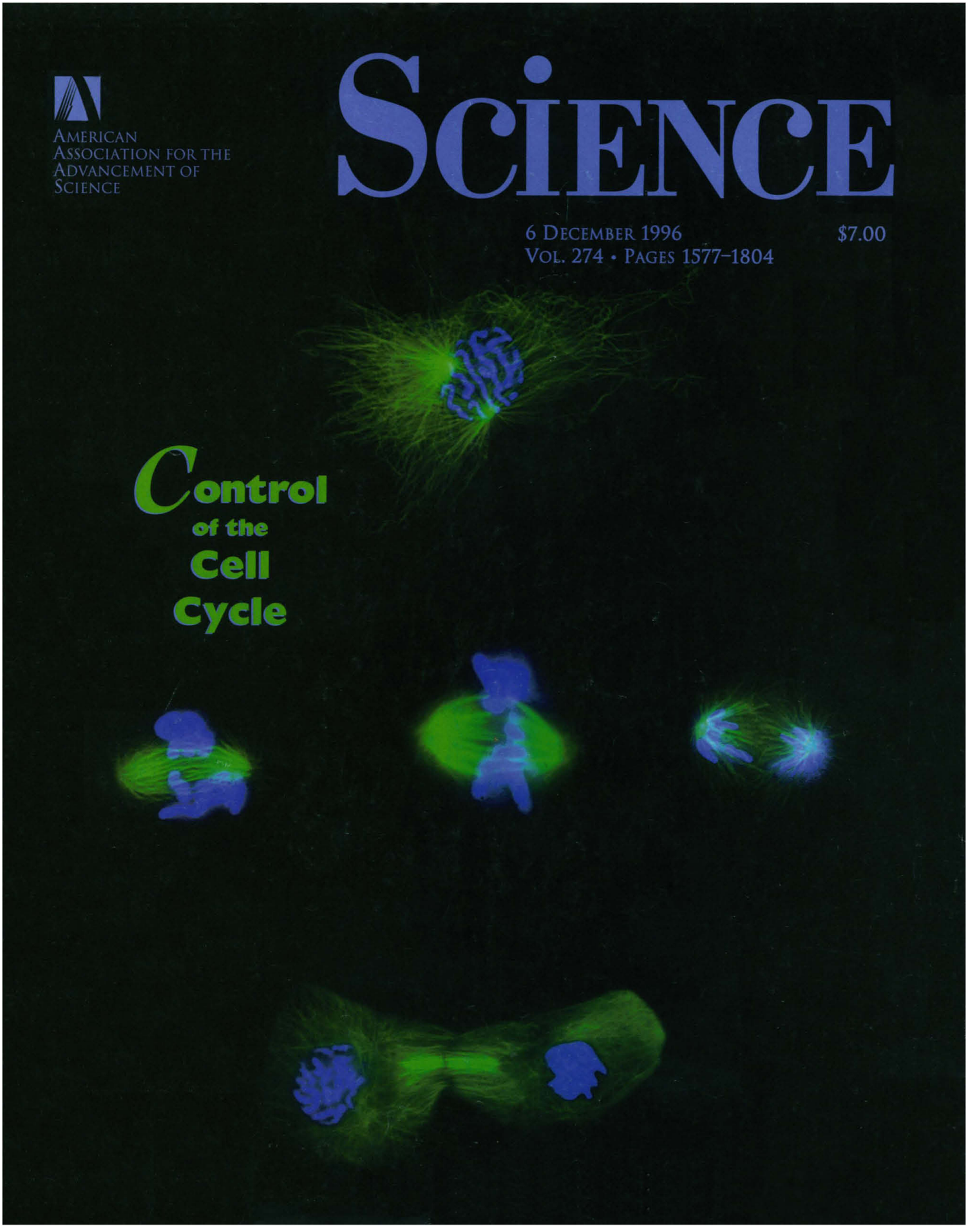

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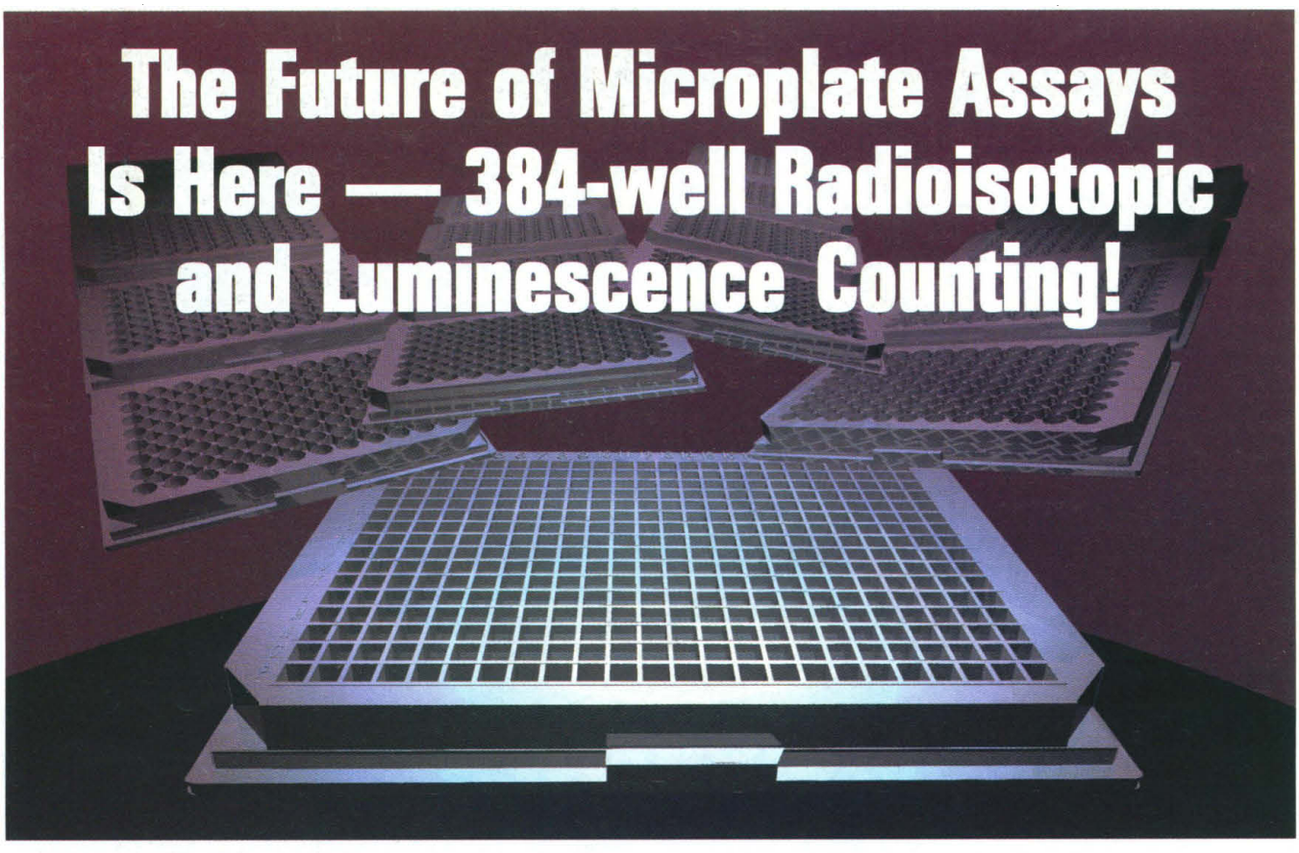

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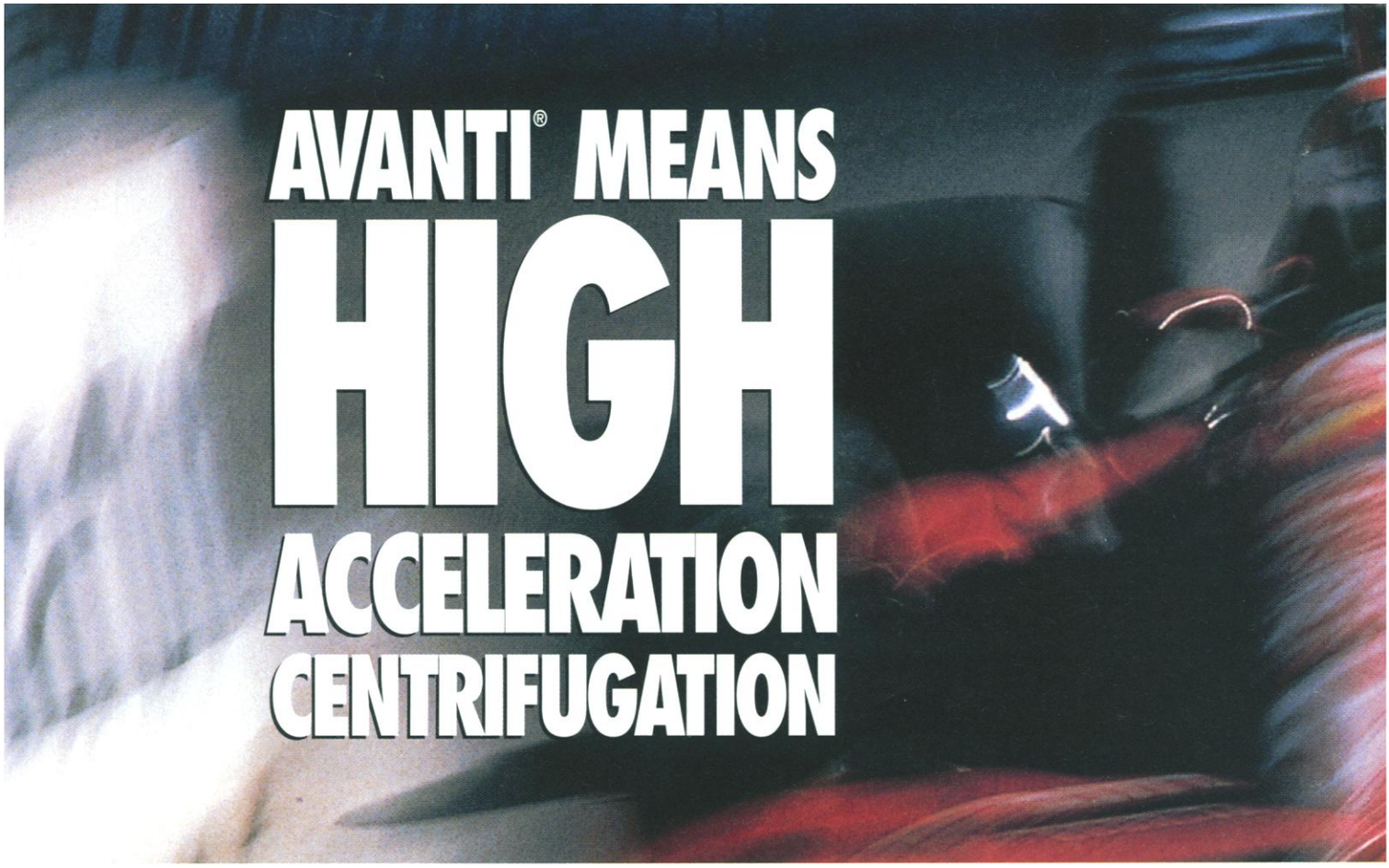
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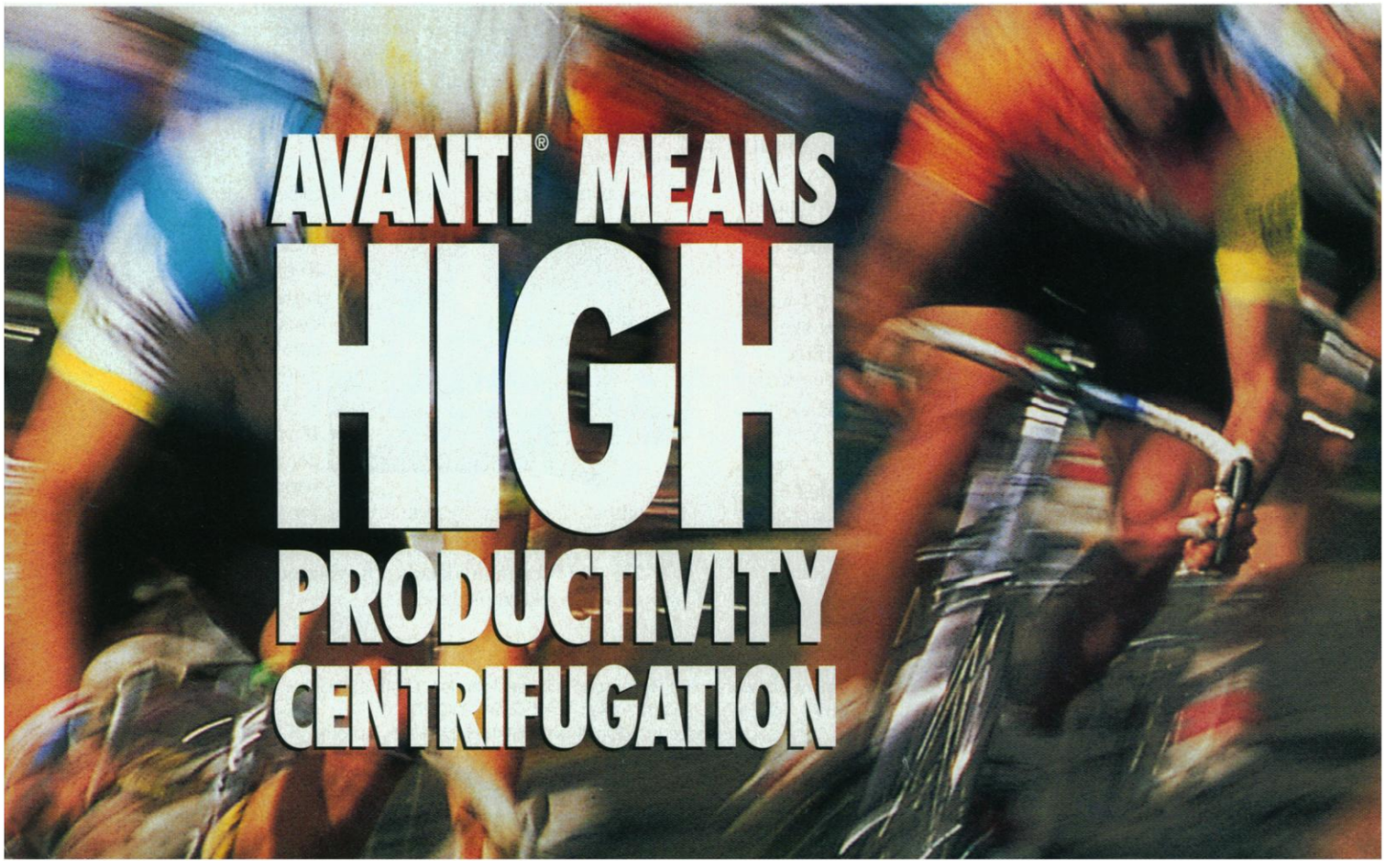
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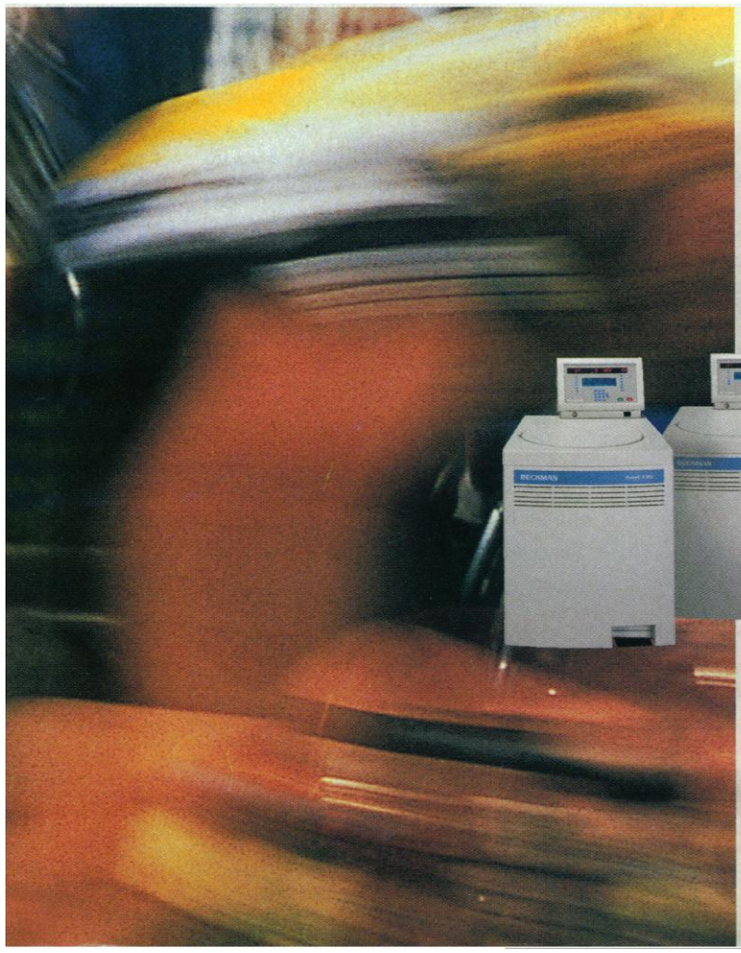

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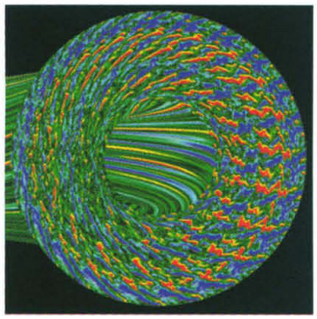
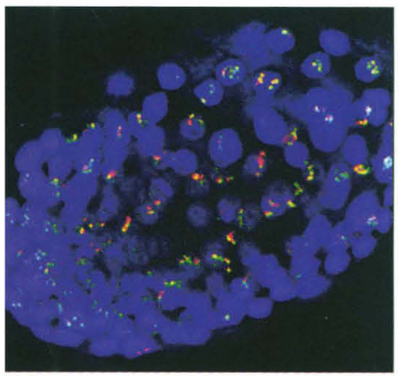


1600
ITER: Fusion or fizzle?



1633, 1732, & 1736
Sex and the compact chromosome

NEWS & COMMENT

RESEARCH NEWS

PERSPECTIVES

CELL CYCLE: ARTICLES

RESEARCH ARTICLE

REPORTS

PROJECT INDEPTH

DEPARTMENTS

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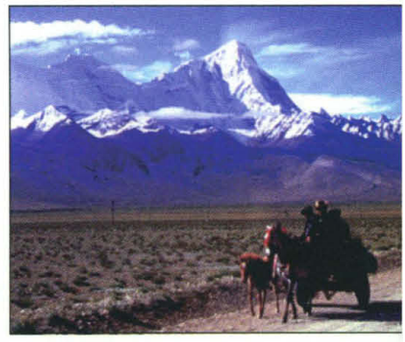
COVER

The stages of mitosis in kangaroo rat cells stained with antibodies to tubulin (green) and a DNA binding dye (blue). The top cell is in prophase, with condensed chromosomes and duplicated centrosomes. The second row shows mitotic spindles and attached chromosomes in prometaphase, metaphase, and late anaphase. Below are two cells in late telophase with decondensing chromosomes. An overview starting on page 1643 introduces a special section that reviews the latest research on cell cycle control. [Image: L. Ma, R. King, M. Kirschner]

TECHNICAL COMMENTS



1684
Views beneath Tibet

◩ Indicates accompanying feature

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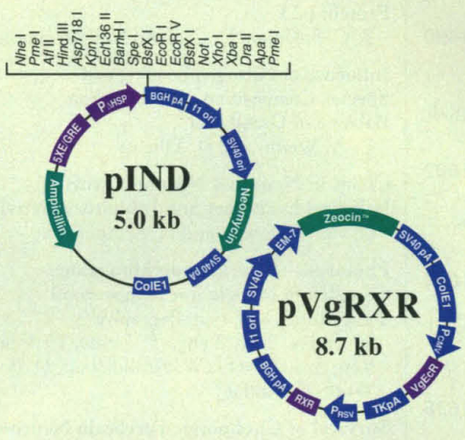
The First Truly Inducible Mammalian Expression System

Invitrogen's new Ecdysone-Inducible Mammalian Expression System is the first system to offer truly low basal expression and high inducibility. Based on a naturally evolved eukaryotic regulatory mechanism that triggers the molting process of insects, ecdysone-responsiveness transfers ideally into mammalian systems (1). This system is entirely unique. It does not rely on prokaryotic operator sites and the artificial nuclear localization of regulatory molecules to control induction as do other regulated systems. This makes the Ecdysone System extremely efficient and easy to use.

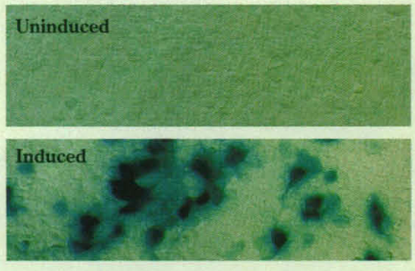
How it Works

For transient transfection and induction, simply clone your gene of interest into pIND, then cotransfect it into mammalian cells with the regulator vector, pVgRXR. Approximately six hours later, treat the transfected cells with the ecdysone analog, muristerone A and begin analysis. Depending on the sensitivity of the assay, you can begin detecting induced expression in as little as two hours. For stable transfection, use dual selection with Zeocin™ and G418.



Tightly Regulated

The slides below show a simple colorimetric assay of 293 cells cotransfected with pVgRXR and pIND/*lacZ* before and after muristerone treatment. This example vividly illustrates the Ecdysone System's tight control and capacity for high inducibility.



Uninduced and induced transiently transfected 293 cells stained with X-gal.

Specificity and Control

Induction is specific–exhibiting no pleiotropic effects on mammalian cells–and dose-dependent–allowing for thorough analysis of gene function through a full range of expression.

Dose-dependent β-galactosidase Induction. 293 cells stably transfected with pVgRXR and pIND/*lacZ* treated with increasing amounts of muristerone A. Equal amounts of isolated protein were separated by SDS-PAGE, blotted and detected by antibody and chemiluminescence.

COMPLETE KIT. The Ecdysone-Inducible Mammalian Expression System has everything you need to get started, including vectors, a positive control, sequencing primers, Zeocin™ antibiotic, and muristerone A. Stable cell lines expressing the regulator (pVgRXR) are also available. Call Invitrogen or visit our web site to learn more about the Ecdysone-Inducible Mammalian Expression System.

1. No, D. *et al.* (1996) *Proc. Natl. Acad. Sci. USA* **93**: 3346-3351.

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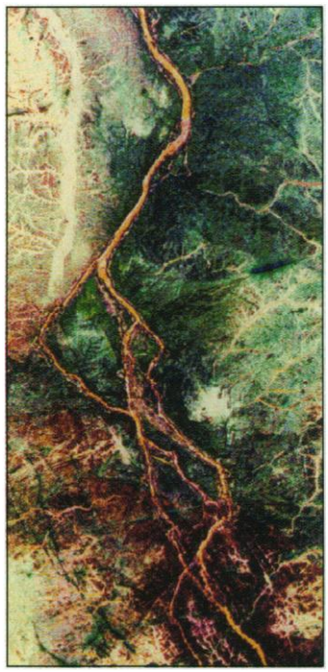
edited by PHIL SZUROMI

Around the bend

Several factors including bedrock geology, tectonics, and climate interact to control river courses. Stern and Abdelsalam (p. 1696) examine the origin of the Great Bend of the Nile River in northern Sudan using radar imagery and geological mapping. The westward bend



reflects the northward flowing segments that follow rock fabrics produced in the Precambrian whereas east-west segments follow Cenozoic faults. Recent uplift in the region may have also led to the westward deflection of the river, forming the great bend.

■

Uplift and melting under Tibet

The ongoing collision of India with Asia has produced the dramatic uplift of the Himalayas and the Tibetan plateau. Understanding the dynamics of this region requires a view of the collision zone at depth. In a series of five reports in this issue (beginning on p. 1684), an international group of researchers report the results of a geophysical survey of the crust underlying the Tibetan plateau. A variety of seismic and electrical observations suggest that the middle crust beneath perhaps large parts of Tibet contains regions of partial melt. The occurrence of melt may be explained by heating as a result of the collision and can help account for some of the interesting dynamics of the Tibetan plateau and adjacent areas.

■

Nanotube brushes grown on silicates

Carbon nanotubes consist of concentric shells of graphitic sheets and have diameters in the nanometer range. Controlled production of the nanotubes, both with regard to their length and diameter and their alignment, is important both for potential applications and for detailed characterization of their properties. Li *et al.* (p. 1701) report a method for producing aligned nanotubes of well-defined length and diameter by using iron particles in mesoporous silica as the catalysts for growing the tubes. Well-aligned arrays of tubes with diameters of 30 nanometers and lengths of 50 micrometers can be grown and can be removed from the substrate to retain aligned tubes.

Gene expression and memory in the brain

Different parts of the brain control different types of memory—thus explicit memory, such as of a place, requires the hippocampus and related medial temporal lobe structures, whereas conditioned fear, an implicit memory, requires the amygdala. In order to study how particular genes affect memory formation, it is necessary to be able to control the timing and location of gene expression within the brain. Mayford *et al.* (p. 1678) combined a forebrain-specific promoter and a tetracyclin transactivator system to control expression of an activated form of calcium-calmodulin–dependent kinase II (CaMKII). Expression of this dominant mutant form of CaMKII in mice led to deficits in hippocampal long-term potentiation (in response to signals in the 5- to 10-hertz range) and in hippocampal-dependent (spatial) memory tasks. These deficits could be reversed by suppression of the transgene. Expression of the transgene only in the lateral amygdyla and the striatum produced a deficit in fear conditioning that could also be reversed at a later stage.

■

Protein piracy

Some DNA viruses, such as herpesviruses, are known to acquire host cell genes. Kaposi's sarcoma–associated herpesvirus (KSHV) is the probable causative agent of KS both in the presence and absence of co-infection with human immunodeficiency virus–type 1 (HIV-1), and Moore *et al.* (p. 1739) have sequenced KSHV genes that encode four viral proteins similar to two human macrophage inflammatory protein (MIP) chemokines, interleukin-6, and interferon regulatory factor. The virally encoded MIP-1, like the human form, inhibits replication of HIV-1 strains dependent on the CCR5 co-receptor. Such viral gene products may interfere with the host cell's defenses.

■

Oral autoantigens and diabetes

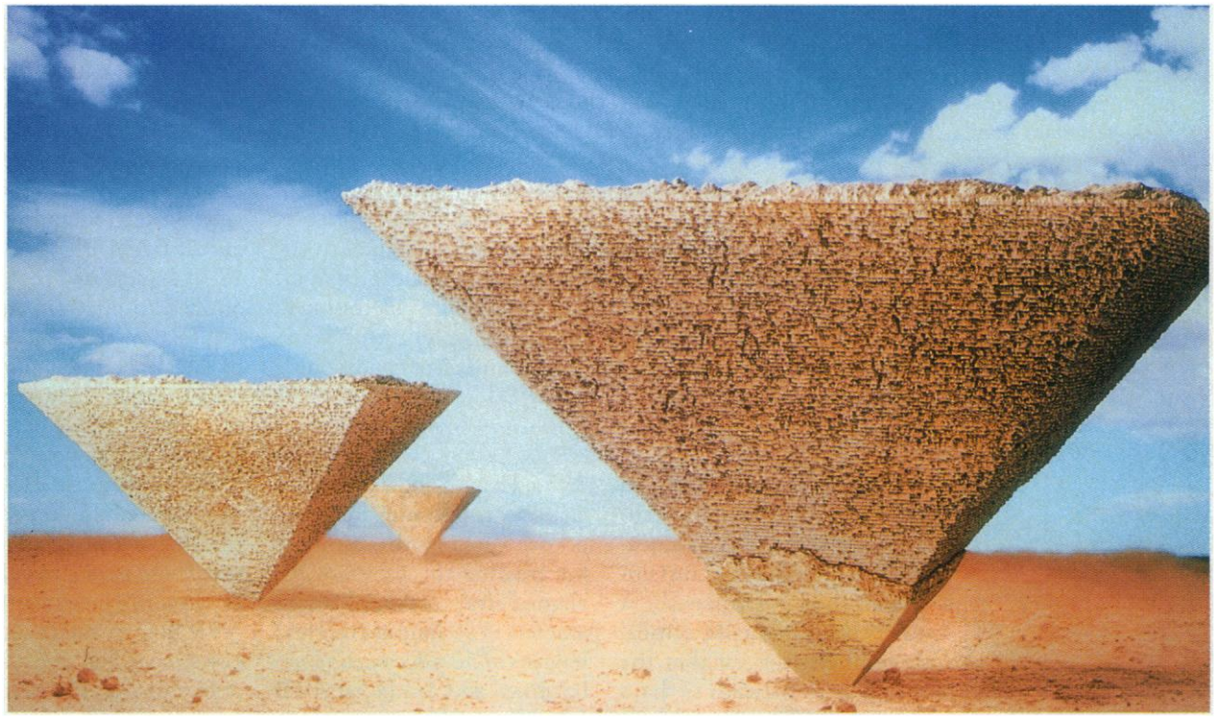
One recent approach to combating autoimmune diseases such as rheumatoid arthritis is to induce tolerance in $CD4^+$ T cells by orally administering the autoantigen. Blanas *et al.* (p. 1707) have found that feeding antigen to mice (in this case, ovalbumin, the "self" antigen in their experimental model of insulin-dependent diabetes mellitus) could produce a cytotoxic $CD8^+$ T cell response that destroyed pancreatic islet cells, a step that could contribute to the onset of autoimmune diabetes. These results indicate that expansion of oral tolerization to other human autoimmune diseases must first consider such potential cytotoxic responses.

■

Overfed grasslands

Addition of limiting nutrients to the environment, such as from fertilizers or detergents, can threaten ecosystems; one example is the phosphorus-driven eutrophication of lakes. The last decade has seen a substantial increase in rates of nitrogen deposition from the atmosphere, and a long-term experiment in Minnesota by Wedin and Tilman (p. 1720) suggests a negative impact for grasslands. Loss of biodiversity was associated with the displacement of native slow-growing grasses (a shift from C_4 to C_3 species), a reduction in the net storage of carbon per additional unit of nitrogen, and a sharp threshold decrease in retention of nitrogen in the soil.

Leave No Stone Unturned.



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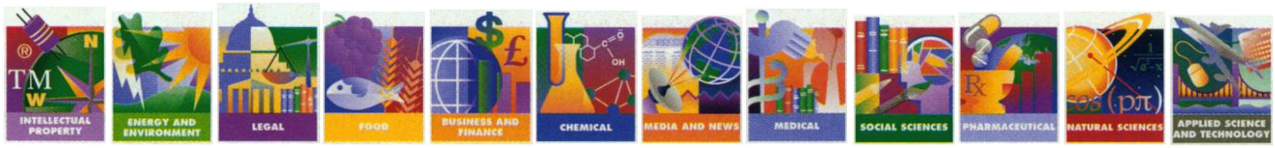

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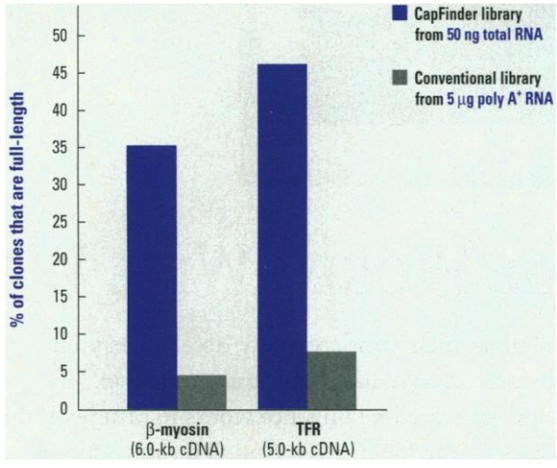

Figure 1. CapFinder cDNA libraries contain a higher percentage of full-length β-myosin and transferrin receptor (TFR) clones than are found in conventional cDNA libraries. CapFinder and conventional libraries were constructed in λgt11 using 50 ng of human skeletal muscle total RNA and 5 µg of poly A+ RNA, respectively. For both genes, the percentage of clones having the full-length sequence was inferred from the ratio of plaques that hybridized with the 5′-end cDNA probe to the number that hybridized with the 3′-end probe on duplicate filters.

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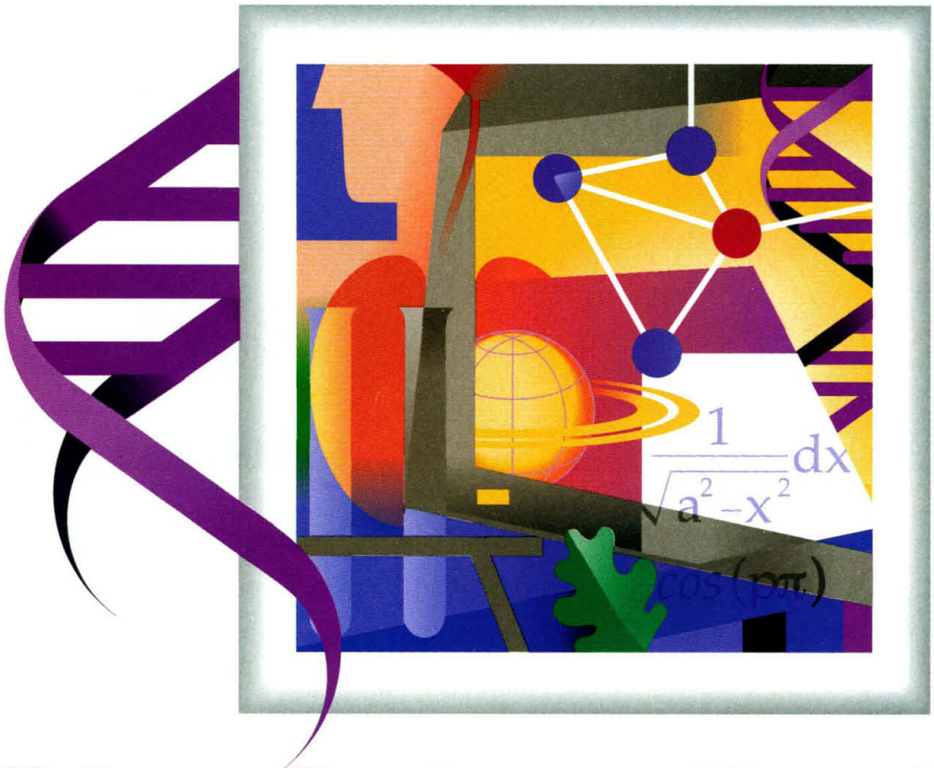

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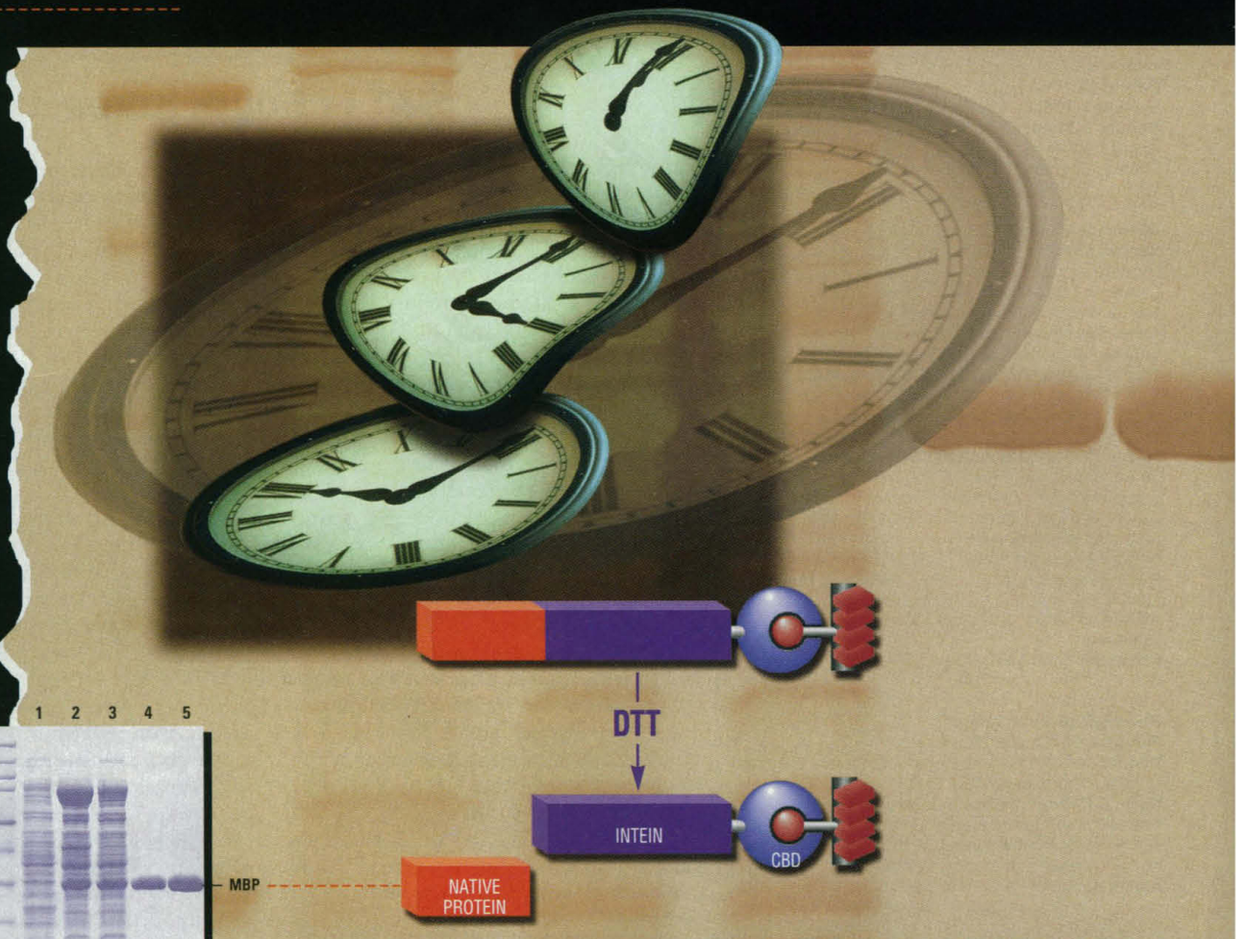

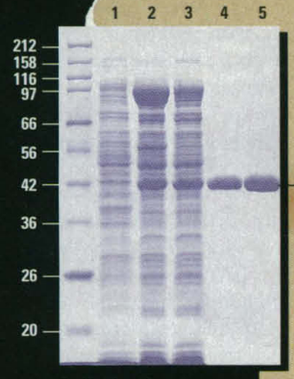

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New Telomerase PCR ELISA Offers Simplified, Nonradioactive TRAP Assay for Measuring Telomerase, A Potential Marker for Cancer Research

Boehringer Mannheim is now offering a Telomerase PCR ELISA for the highly sensitive, nonradioactive detection of telomerase activity in extracts from cell cultures and tissue samples.

Telomerase as an important parameter in cancer research

Telomeres, the specialized DNA/protein structures at the end of eukaryotic chromosomes, contain tandemly repeated DNA sequences that are believed to protect genomic DNA from degradation and deleterious recombination events. During normal somatic cell proliferation, telomeric ends are progressively shortened with each replication cycle, which may play a role in limiting the proliferative capacity of normal cells. Germline cells, many tumor cells, and "immortalized" cell lines are believed to circumvent this telomere shortening using telomerase, a ribonucleoprotein that adds new repeats to the ends of chromosomes. Telomerase activity has recently been identified in many cancers (e.g., prostate cancers [1], advanced-stage breast cancers [2], neuroblastomas [3], and primary lung cancer tissues [4]) that have been confirmed by other methods (*e.g.*, histochemical staining). Thus, telomerase reactivation may allow cells to escape from the proliferative limitations of cellular senescence and could be further investigated as a potential marker for the development of malignant tumor cells.

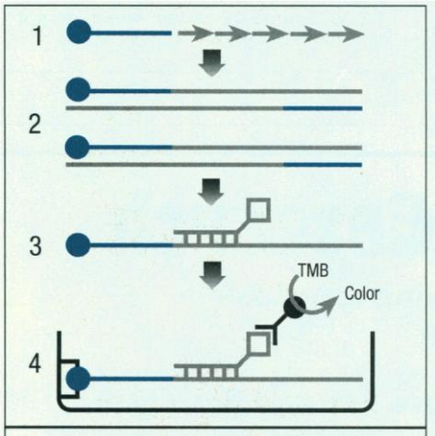

Figure 1. Detection of telomerase activity with the Telomerase PCR ELISA.

Step 1. Telomerase, if present, adds multiple 6-nucleotide telomeric repeats to a biotinylated synthetic primer.

Step 2. The telomerase reaction product is amplified by PCR, using a biotinylated primer.

Step 3. After denaturation, the PCR product hybridizes to a digoxigenin-labeled probe specific for the telomeric repeat.

Step 4. The DNA hybrid binds to a streptavidin-coated microtiter plate, and anti-digoxigenin-peroxidase and TMB substrate generate a colored product measurable with a microplate reader.

Note: If desired, the TRAP reaction product from Step 2 can also be detected by the traditional gel electrophoresis method.

Telomerase PCR ELISA improves upon previous TRAP assays

Telomerase activity is most frequently detected by the Telomeric Repeat Amplification Protocol (TRAP) of Kim *et al.* (5), in which the telomerase-reaction product is amplified by PCR. However, the conventional TRAP assay achieves full sensitivity only when performed with a hazardous radioactive label, and visualization of results requires time-consuming gel electrophoresis and autoradiography. The new Telomerase PCR ELISA*,† combines a one-step/one-tube TRAP assay with nonradioactive detection in a highly sensitive photometric ELISA (Figure 1).

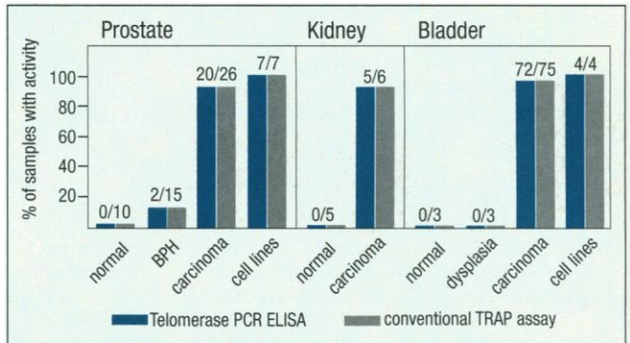

Figure 2. Correlation of results obtained with the Telomerase PCR ELISA and conventional, radioisotopic TRAP assays. Samples from known carcinomas, normal specimens (negative control), benign prostatic hyperplasia (BPH) specimens, and immortalized cell lines were tested with the Telomerase PCR ELISA and conventional, radioisotopic TRAP assays. In all sample types, the methods were able to identify the same number of samples featuring telomerase activity. Data provided by M. Müller and R. Heicappell (6) and by H. J. Sommerfeld.

Easy-to-use ELISA delivers results in less time

The Telomerase PCR ELISA delivers results within 6 hours, eliminating the need for laborious, time-consuming gel electrophoresis and autoradiography techniques. Its ready-to-use TRAP reaction mix (telomerase substrate, amplification primers, nucleotides, *Taq* DNA polymerase, reaction buffer) eliminates the need to prepare multiple solutions and minimizes the risk of assay failure caused by contamination. Up to 96 TRAP reactions can be simultaneously analyzed with an ELISA plate reader.

Sensitive results correspond closely with those of radioactive TRAP assays

Besides avoiding the use of hazardous radioisotopes, the Telomerase PCR ELISA produces sensitive results comparable to those of the radioisotopic TRAP assay (Figure 2). The kit's optimized detection probe and hybridization conditions maximize both specificity and sensitivity. Additionally, optimized primer sequences eliminate the need for "hot start" PCR while avoiding amplification artifacts (*e.g.*, primer dimers).

The Telomerase PCR ELISA is currently available

The Telomerase PCR ELISA (96 tests; Cat. No. 1 854 666) is now available from Boehringer Mannheim Biochemicals representatives. Additional information can also be found at http://biochem.boehringer-mannheim.com.

References:

1. Sommerfeld, H. J. *et al.* (1996) *Cancer Research* **56**:218-222.
2. Hiyama, E. *et al.* (1996) *J. National Cancer Institute* **88**:116-122.
3. Hiyama, E. *et al.* (1995) *Nature Medicine* **1**:249-255.
4. Hiyama, K. *et al.* (1995) *J. National Cancer Institute* **87**:895-902.
5. Kim, N. W. *et al.* (1994) *Science* **266**:2011-2015.
6. Müller, M. *et al.* (1996) *Int. J. Oncology* **9**: *in press.*

†Licensed from Geron Corporation. Patents pending.

*Purchase of this product is accompanied by a limited license to use it in the Polymerase Chain Reaction (PCR) process in conjunction with a thermal cycler whose use in the automated performance of the PCR process is covered by the up-front license fee, either by payment to Perkin-Elmer or as purchased, i.e., an authorized thermal cycler.

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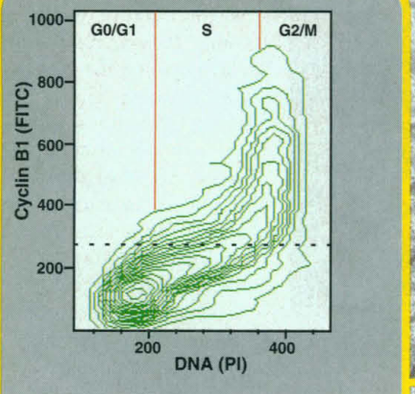


Flow cytometric analysis of cyclin B1. Proliferating MOLT-4 leukemia cells were stained with FITC-conjugated anti-cyclin B1 (Cat. #1371KK). DNA was stained with Propidium Iodide. Cyclin B1 expression is low in G0/G1, increases in late S and is maximal in G2/M. Dotted line: negative (isotype control) staining.

Cyclins

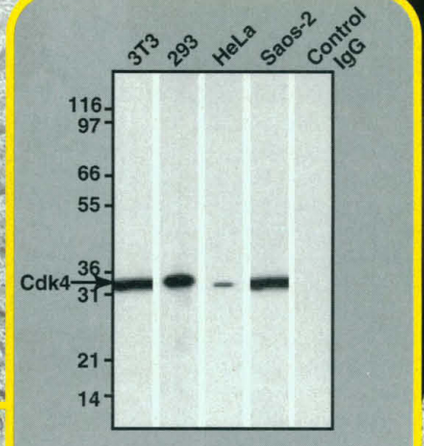
- Cyclin A
- Cyclin B1
- Cyclin D1
- Cyclin D2
- Cyclin D3
- Cyclins D2 & D3
- Cyclin D1,D2 & D3
- Cyclin E
- Cyclin H

Cdks

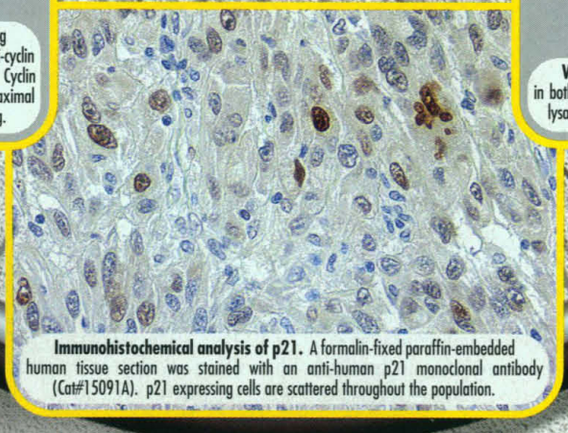
- Cdk1
- Cdk2
- Cdk3
- Cdk4
- Cdk5
- Cdk6
- Cdk7

Cdk Inhibitors

- p16
- p18
- p19
- p21
- p27



Western blot analysis of Cdk4. Cdk4 was identified in both mouse (3T3) and human (293, HeLa, and Saos-2) cell lysates using an anti-Cdk4 monoclonal antibody (Cat #13961).



Immunohistochemical analysis of p21. A formalin-fixed paraffin-embedded human tissue section was stained with an anti-human p21 monoclonal antibody (Cat#15091A). p21 expressing cells are scattered throughout the population.

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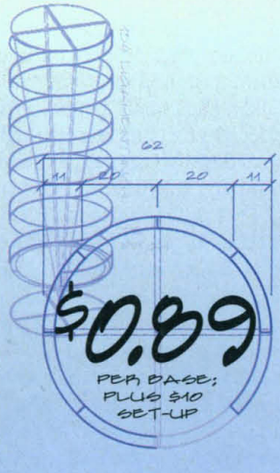

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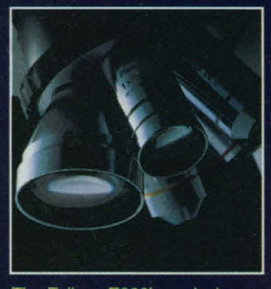

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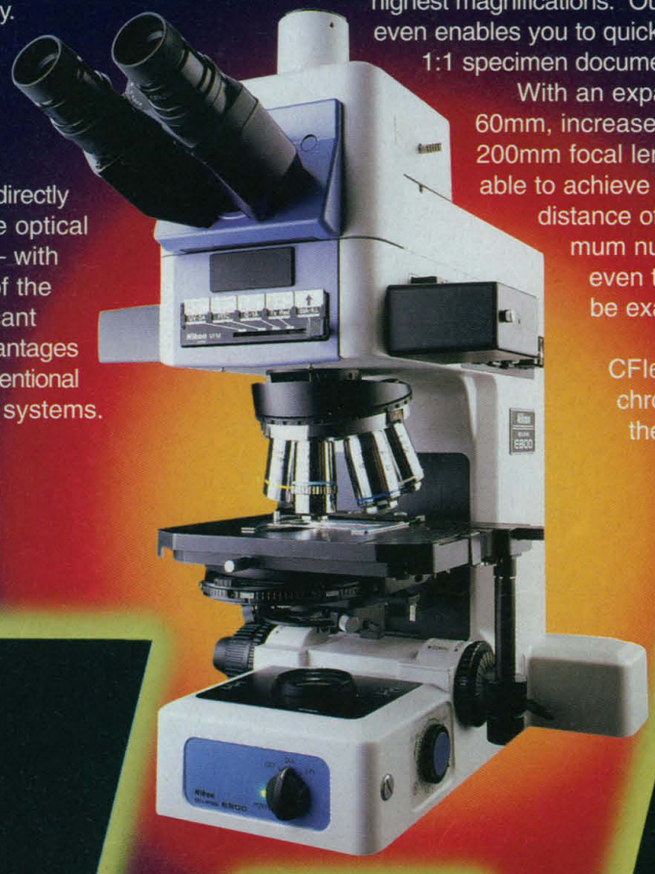

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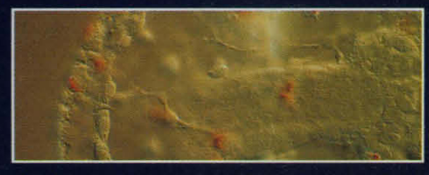

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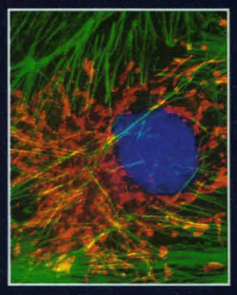

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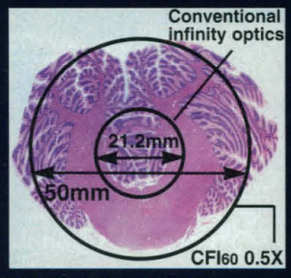

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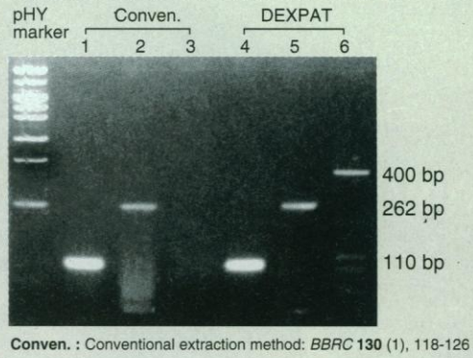
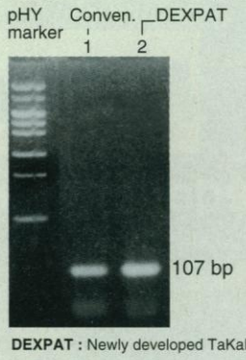
DNA Amplification from Paraffin-embedded Tissues of Colon Cancer after a10-year Preservation:

The DEXPAT™ resulted in excellent PCR amplification with greater yield and longer extension than the conventional method. With DEXPAT™, DNAs were extracted as PCR ready templates which were then amplified with *Ex Taq*. Amplifications of DNAs obtained with the conventional extraction method were simultaneously conducted and compared. DNAs were extracted from two pieces of preserved tissue: Each piece was dissected into a size of 10 μm thick and 1 cm^2 area.

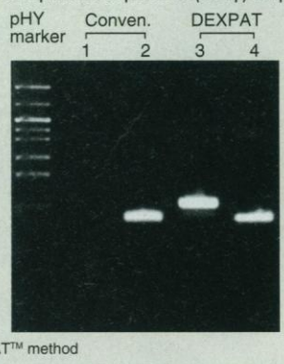
1. Amplification of β-globin (110 bp, 262 bp, 400 bp)



2. Amplification of K-*ras* 12 (107 bp)



3. Amplification of p53 exon5 (273 bp) and p53 exon6 (207 bp)



Conven. : Conventional extraction method: *BBRC* **130** (1), 118-126 (1985) **DEXPAT** : Newly developed TaKaRa DEXPAT™ method

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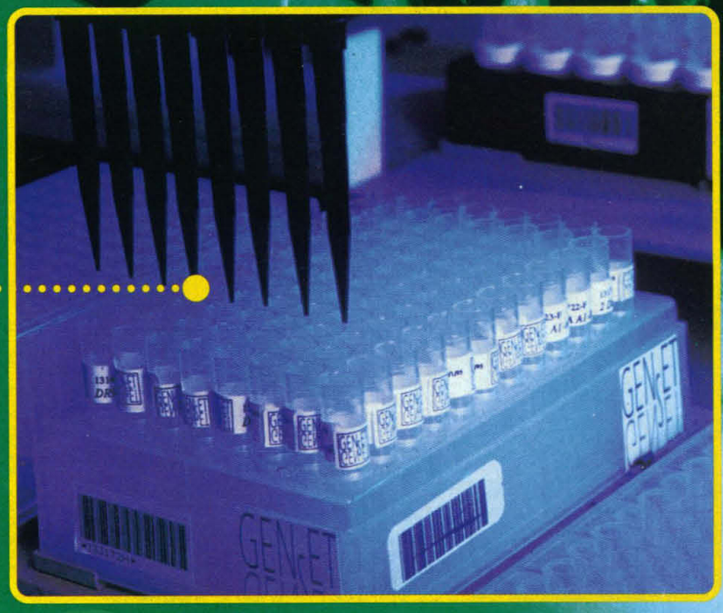

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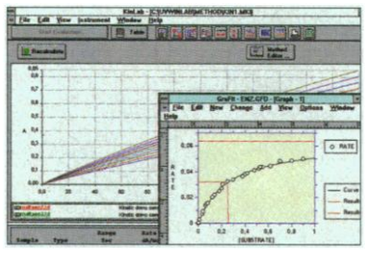

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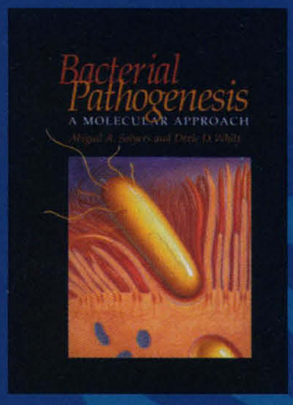

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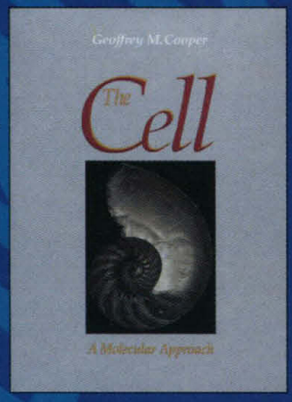

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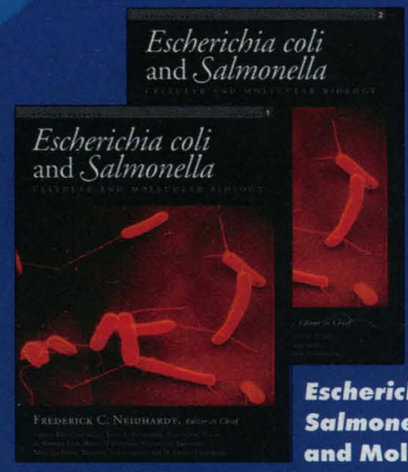

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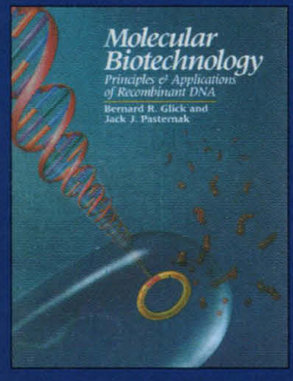

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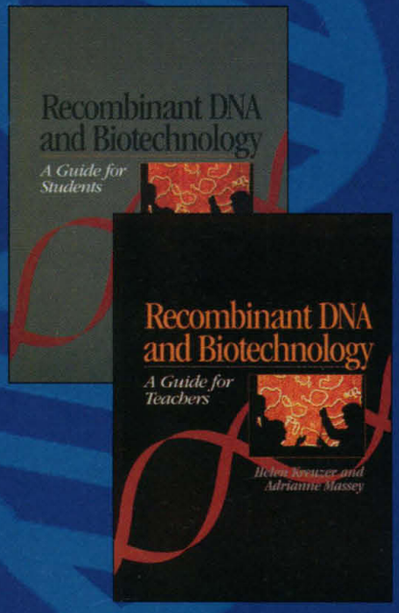

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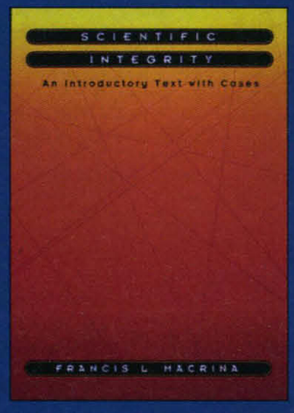

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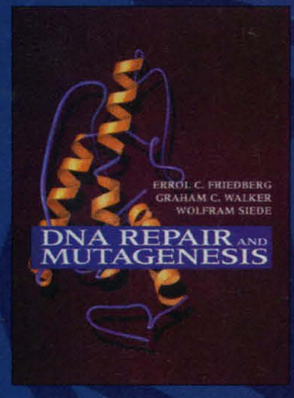

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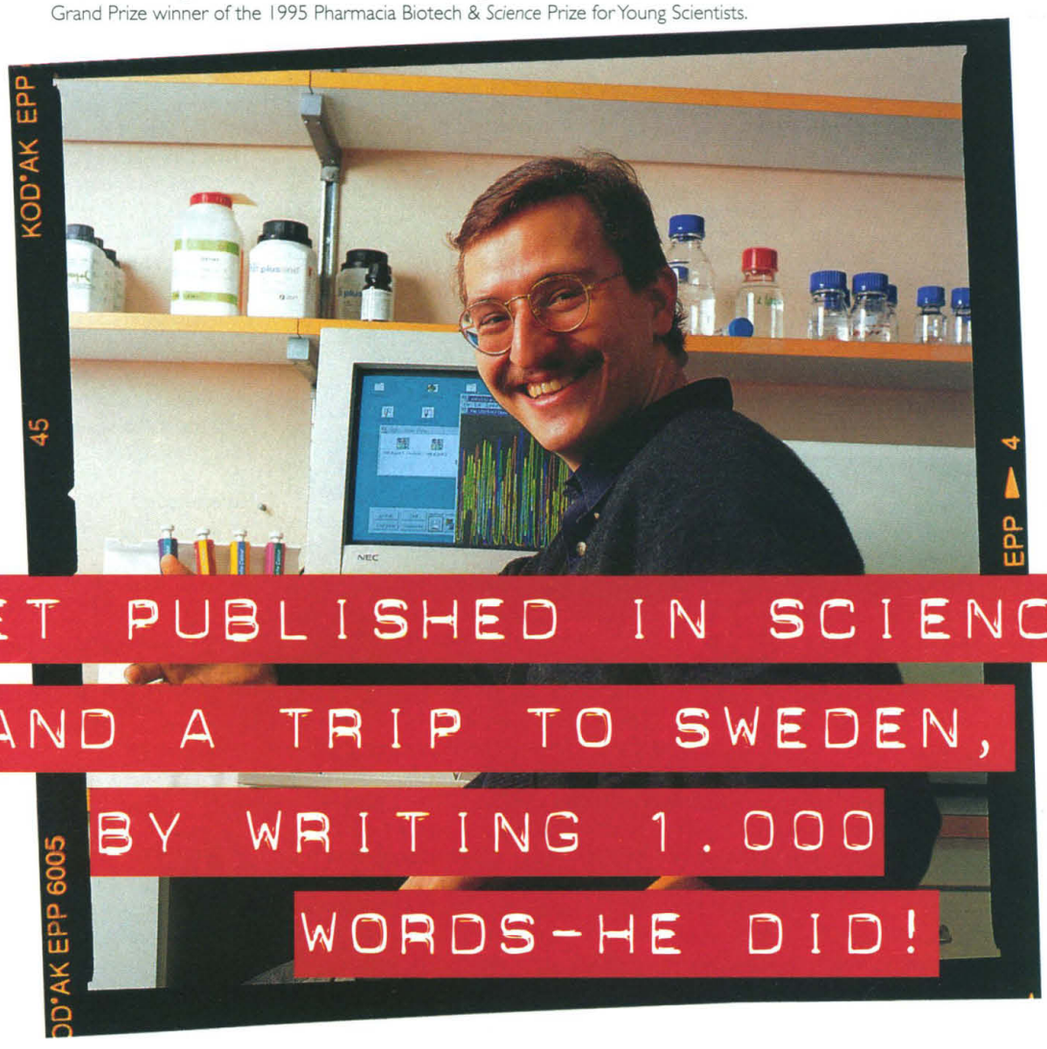

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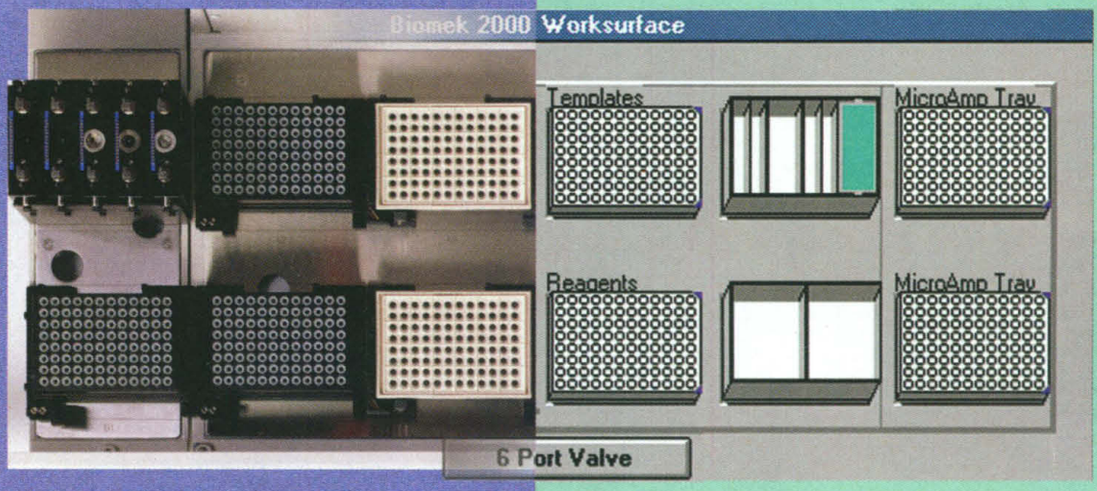

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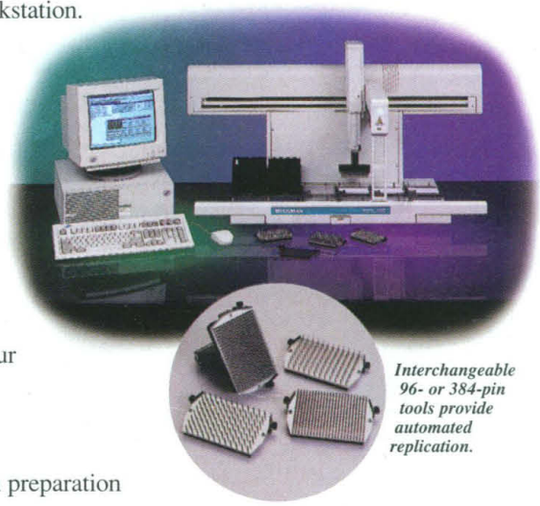

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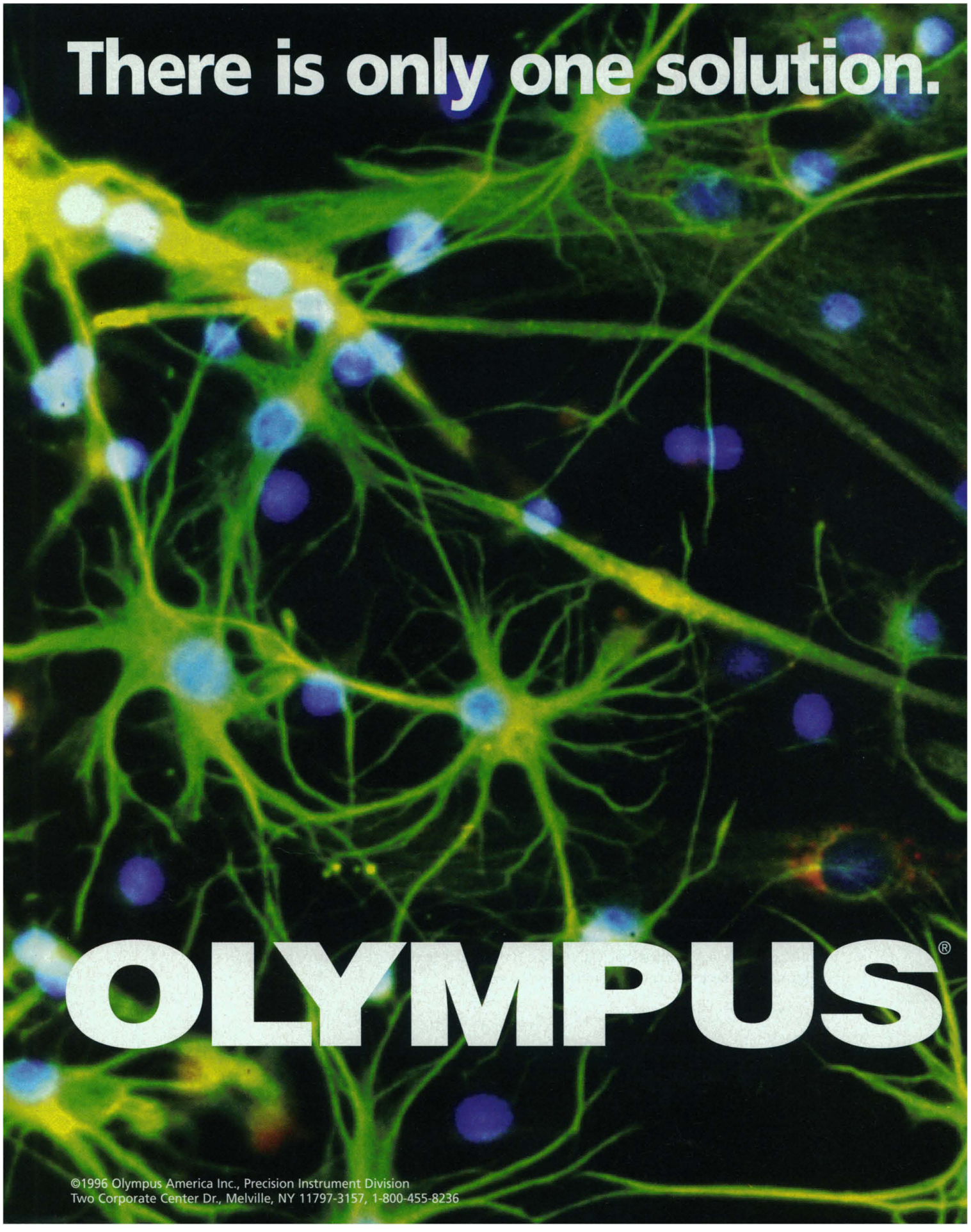
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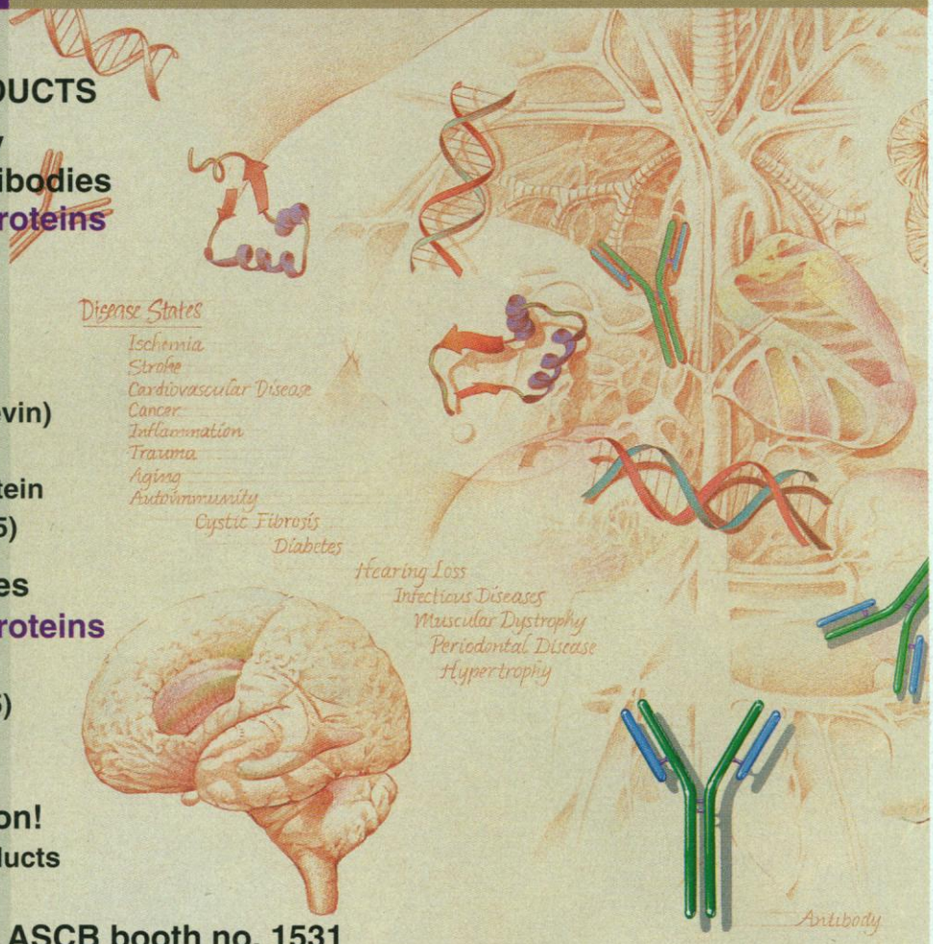

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