2 June 2000

# Science

Vol. 288 No. 5471
Pages 1537–1692 $8

American Association for the Advancement of Science

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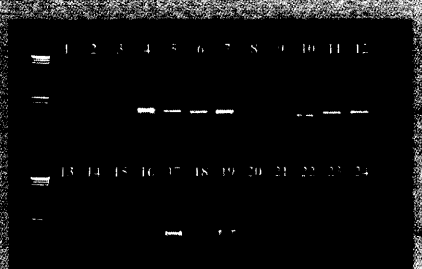

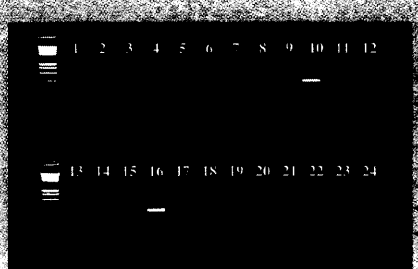

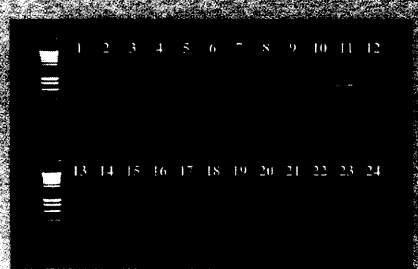

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VOLUME 288 2 JUNE 2000 NUMBER 5471

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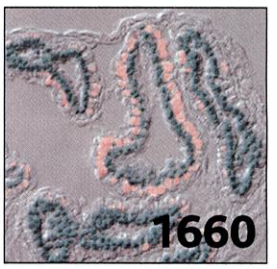
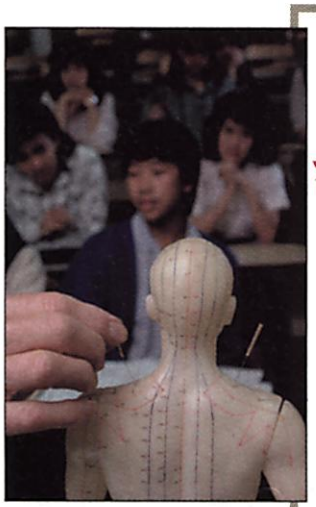



**COVER** The progeny from adult mouse brain neural stem cells contributes to the generation of kidney tubules after injection into the early chick embryo. Kidney tubule cells express Pax2, and the presence of this marker (red) in nuclei of neural stem cell–derived cells (blue labeling in cytoplasm) indicates that they have the potential to generate nonneural cells. Image width, 280 micrometers. [Photograph: D. L. Clarke]



**1568**
Healing alternative medicine

## NEWS

### NEWS OF THE WEEK



### NEWS FOCUS



## RESEARCH

### RESEARCH ARTICLE



### REPORTS






### DEPARTMENTS



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SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals Mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices.  Domestic individual membership and subscription (51 issues): $112 ($62 allocated to subscription). Domestic institutional subscription (51 issues): $340; Foreign postage extra: Mexico, Caribbean (surface mail) $55; other countries (air assist delivery) $90. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. Publications Mail Agreement Number 1069624. **Printed in the U.S.A.**

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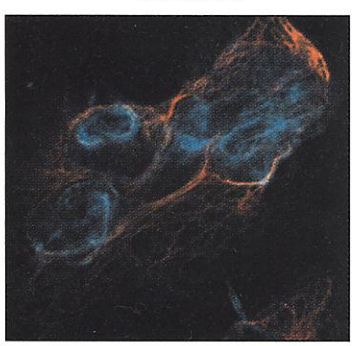

**1613**
Regulation of flowering


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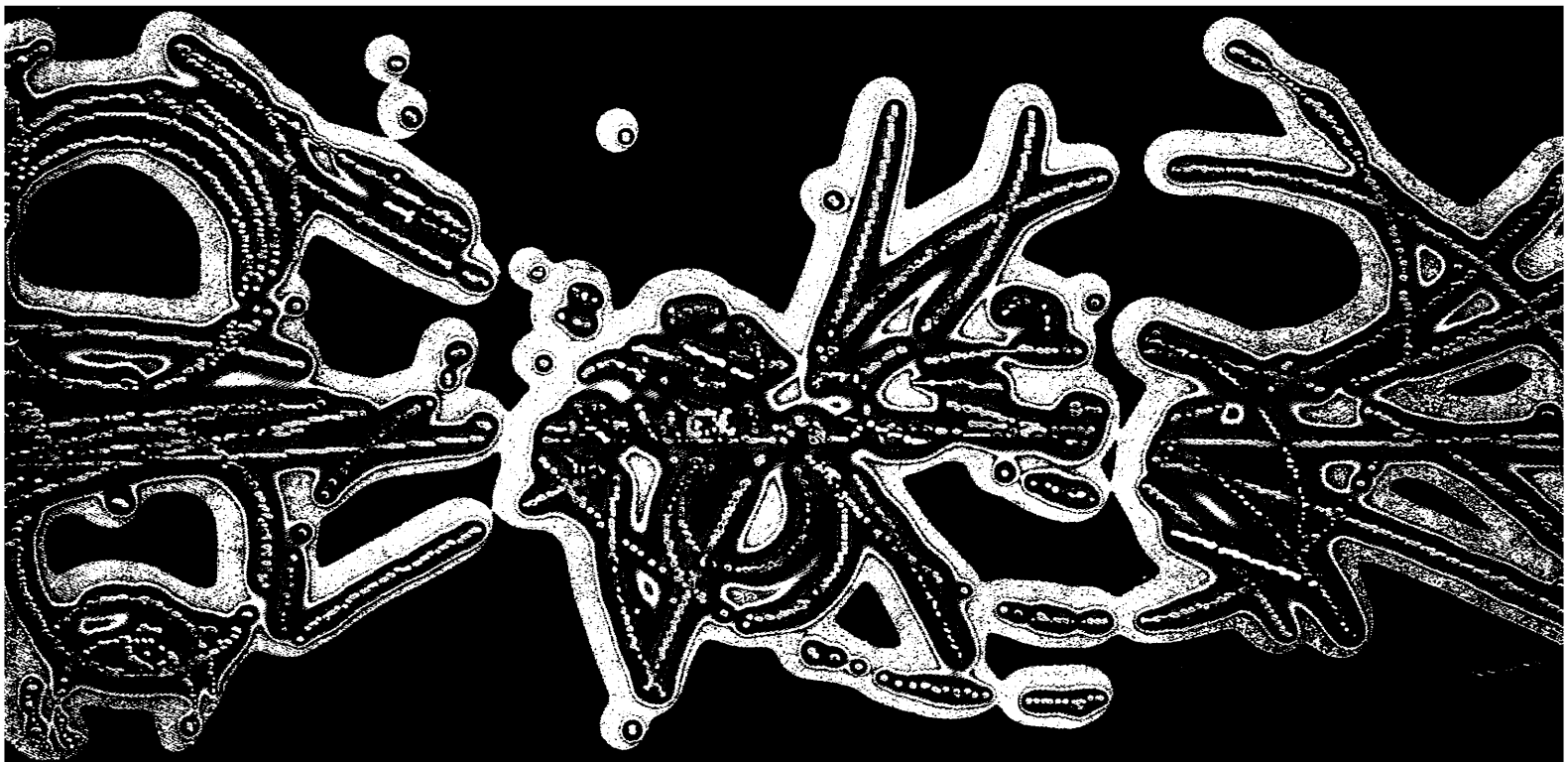

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Above image: a photographically colored version of the original electronic image obtained from UA1 detector at CERN, Geneva, showing tracks of an electron-positron pair.

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THE MJ RESEARCH NOTEBOOK

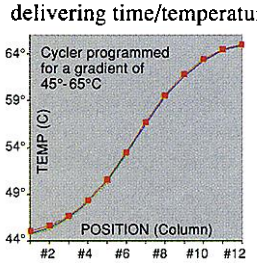
*Volume IX...No. 3* *A Bulletin of Technological Advance in Molecular Biology* *Spring 2000*

# *Gradient Calculator Especially Useful*

## Easy to Transfer "Golden" Parameters to Actual Protocols

Most researchers would agree that gradient cyclers are great in concept—but their utility is significantly compromised if an optimized protocol does not transfer well to normal, non-gradient operation. This "Achilles heel" of gradient cyclers can often be traced to imprecise knowledge of either incubation time or incubation temperature during the gradient step. Whatever technology is used, there will always be lags—often not well known—before samples reach the new temperature.

MJ has long had an excellent reputation for delivering time/temperature control with precision, so extra efforts were expended to address these issues. Thus time control includes "dynamic ramping" (see below), while temperature control incorporates a new software feature called the "gradient calculator".



Reported temps (dots) vs. independently acquired thermal data in 4 cyclers (lines).

This calculator is so precise and accurate that it reports the temperatures in individual columns to within ±0.4°C of the NIST standard, making transfer of values to normal operation *very* reproducible. Just look above how reported temperatures from the gradient calculator superpose *almost perfectly* with independent NIST-traceable data from 4 different cyclers.

# NEW GRADIENT HELPS OPTIMIZE ANNEALING AND DENATURATION


DNA Engine™, with the thermal gradient shown in artificial colors from data collected by an IR camera.

## Optimized Denaturations Surprisingly Important

It is well known in the biological community that DNA amplification reactions should have optimized annealing temperatures for best results. Denaturation is quite important as well—but only the savvy optimize this step.

Too bad. MJ's scientific staff finds that denaturation often leads to problems. Use of a lower denaturation temperature, such as 90°-92°C, is generally recommended whenever possible. Not only does it preserve enzymatic activity for later cycles, it also reduces breakdown of fluorescent dyes in cycle sequencing. On the other hand, higher temperatures, such as 95°-96°C, may be required for GC-rich templates from organisms such as Mycobacteria.

# ALL EXISTING DNA ENGINES & TETRADS CAN BE UPGRADED

## Standard Feature on New Thermal Cyclers

WALTHAM, Mass. — MJ RESEARCH is pleased to announce the introduction of an advanced gradient feature that is now standard on all DNA Engine & Tetrad thermal cyclers. This powerful new function allows precision thermal gradients as high as 24°C to be developed across 96-well blocks, at any temperature between 30° and 105°C. This greatly assists in developing robust protocols, for the optimal annealing and denaturation temperatures give strong results without lots of "ampli-schmutz" or other unwanted artifacts appearing in the gel.

Many reactions benefit from careful temperature optimization, especially sensitive ones, such as dye-terminator cycle sequencing. GC-content, length of molecule, concentration of magnesium—all these lead to differences in optimal "heat" for annealing and denaturation. This is why empirical experiments can almost always enhance even the *best* calculations for $T_m$.

But who wants to do a dozen runs of slightly variant protocols? Gradient cyclers make this chore much easier by allowing a dozen different incubation temperatures in a single run. The user simply selects a range of temperature, and the cycler does the rest. The optimal temperatures become obvious in the gel—with thick "meaty" bands unbracketed by artifact.

### How to Get Upgrade

In a nutshell, visit the MJ website. For DNA Engines manufactured after 1/1/99, the gradient feature is a simple software upgrade that is provided free and can be installed by users. For older DNA Engines or Tetrads, a new logic board is also required, and this upgrade is available inexpensively from MJ or its distributors.

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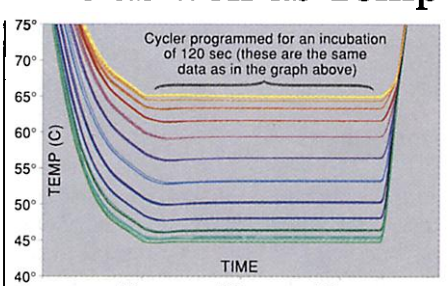
# Precision Control of Time as well as Temp

## "Dynamic Ramping" Incubates Each Sample for Same Period

In some gradient cyclers, the gradients develop gradually. When cooling to an annealing gradient, for example, the highest temperature stabilizes long before the lowest one does. This means that the time spent at incubation is different at each temperature—thus two critical parameters are being varied at the same time.

Not so with MJ cyclers. Careful engineering has led to "dynamic ramping" where each column of wells ramps at a different rate, for ramp rates are much less critical. The results are consistent incubation times column-to-column, with only temperature varying among samples.



Data from four cyclers are superposed in this graph, with each trace representing the average temperature measured in a column of wells. Note the consistency of incubation periods, the cycler-to-cycler reproducibility (each trace is made up of *four* separate lines), and the even spread of incubation temperatures between the programmed targets of 45° and 65°C.

### COUPLING EXCITATIONS

Light harvesting is a key step in photosynthesis in which numerous chromophores are coupled to collect light and then funnel energy to the reaction centers. Lidzey *et al.* (p. 1620) have studied an analogous system in which spatially separated layers of different organic dye molecules are contained within an optical microcavity. Electronic excitations of the dyes (excitons) can couple to the photon mode of the microcavity to form new modes that are mixtures of all three states. Coupling can be seen between the excitons at room temperature despite an energy separation of 60 millielectron volts. These model systems of energy transfer may also have applications in optoelectronic devices.

### LIGHT-DRIVEN LIQUIDS

Whether a liquid will wet a surface or form droplets depends in part on the free energy of surface. Ichimura *et al.* (p. 1624) have modified surfaces with a compound that contains photochromic azobenzene units. The photoinduced *cis-trans* isomerization of these groups changes the contact angles that droplets make with the surface. For hydrophobic liquids and even some nematic liquid crystals, millimeter-sized droplets could be propelled by creating surface gradients with asymmetric light pulses. The authors used this effect to move glass beads through derivatized glass tubes.

### GALAXY METAMORPHOSIS

Recent observations of distant clusters of galaxies suggest that older clusters are dominated by lenticular galaxies (S0 galaxies) that have lost all of their atomic hydrogen gas and that show no evidence for recent star formation. Quilis *et al.* (p. 1617) present results from a high-resolution, three-dimensional model which show that S0 galaxies can form when spiral galaxies move through a hot, ionized intracluster medium. Their simulations, which included shock-wave effects and viscous stripping of the galactic halo, produced S0 galaxies within 100 million years from spiral galaxies like the Milky Way and provide a mechanism that can explain the changing galaxy morphology in clusters.

### POST-STISHOVITE IN THE SHERGOTTY METEORITE

Examinations of the Shergotty meteorite, thought to originate on Mars, have revealed a checkered history of dynamic deformation from repeated impacts that led to its ultimate transport to Earth. Study of its mineralogy and textures are important to unravel its complex origin to improve our understanding of planetary interactions and evolution. El Goresy *et al.* (p. 1632) have characterized an additional silica phase more dense than stishovite (a post-stishovite phase) that has a monoclinic structure interwoven with another post-stishovite phase and silica glass. Post-stishovite phases form at pressures above 48 gigapascals (GPa) from stishovite, and the new post-stishovite phase should be stable between 70 to 85 GPa. Such high pressures are inconsistent with other observations of Shergotty that suggest a peak impact pressure of about 30 GPa. The post-stishovite phases may form through a metastable reaction, which may require a peak pressure of as low as 40 GPa, however, and thus Shergotty may have been shocked to an intermediate pressure range.

### IRON VIBRATIONS

Earth's core is thought to be composed predominantly of hexagonal close-packed (hcp) iron. To explain the seismic properties of the core, experimentalists and theorists have tried to extrapolate the elastic properties of hcp iron to the high pressures and temperatures, yet discrepancies remain. Merkel *et al.* (p. 1626) have measured the one Raman-active mode of hcp iron up to pressures of 150 gigapascals; ultrapure diamond anvils were used to avoid background luminescence and scattering that could obscure the Raman spectrum. Their results suggest that the shear wave anisotropy at core conditions should vary by about 35%, which should provide geophysicists with a useful parameter to distinguish structural versus chemical changes reflected in varying seismic waves that sample the core.

### FLOWERS EMPOWERED

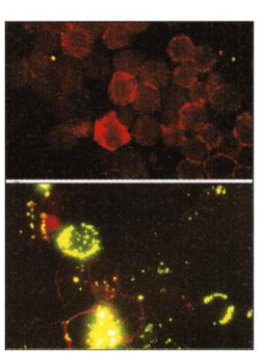
In order to better understand the transition from vegetative growth to flowering, Samach *et al.* (p. 1613; see the Perspective by Devlin and Kay) investigated genes directly regulated by the gene *CONSTANS* (*CO*), itself known to promote flowering of *Arabidopis* in response to longer days. With the use of a conditional overexpression system, four genes were identified that are directly regulated by CO. Of these four, *FT* and *SOC1* are regulated by a balance of CO and FLC activity, itself part of the vernalization response. The other two genes affect patterns of development in the stem and the flower. Thus, a network of regulatory pathways is revealed that not only promotes development of floral structures but that also integrates day length, response to chilling, and age of the plant into the ultimate developmental decision of when to begin flowering.

### STEM CELL SECRETS

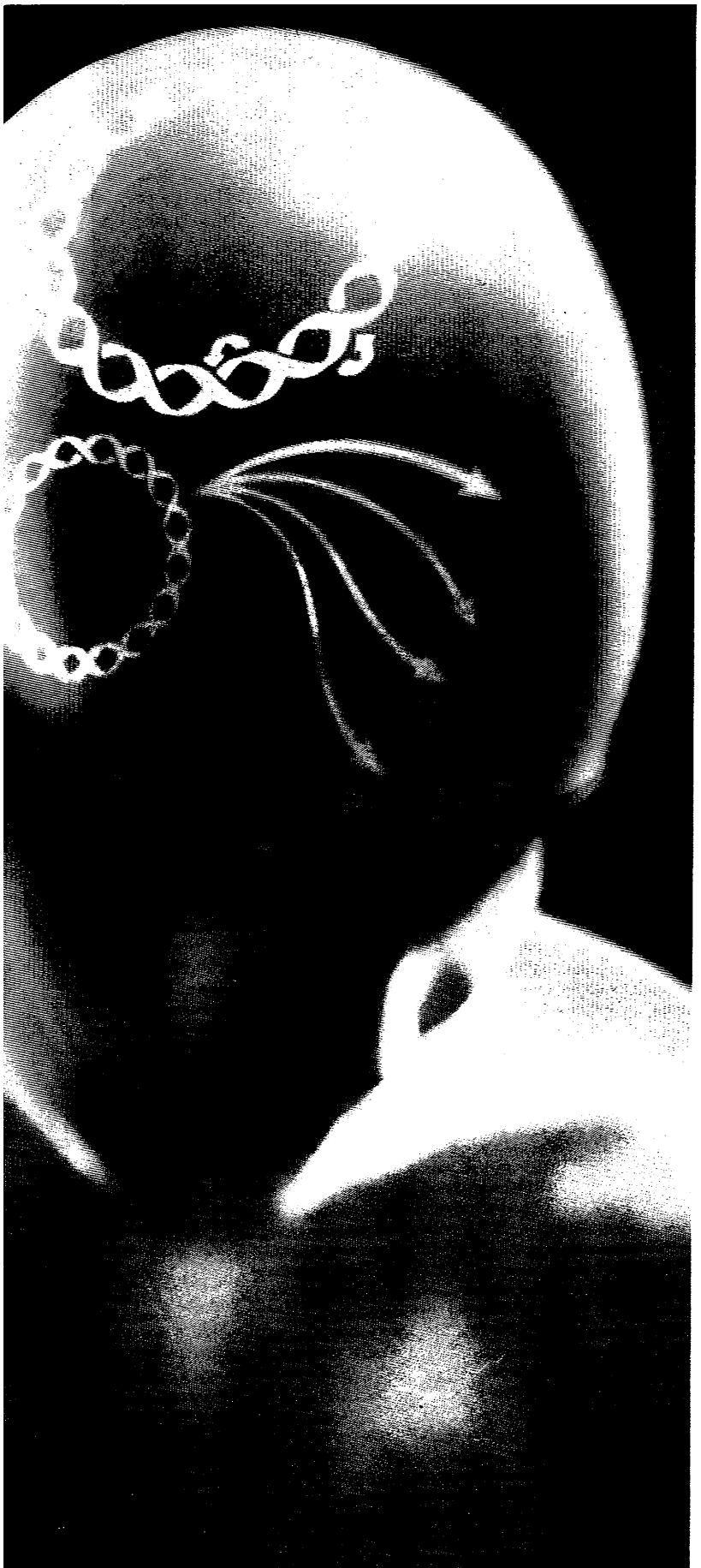
Despite an apparent lack of phenotype, stem cells are able to give rise to many other types of cells. The types of cells they can become, and some genetic insights into how a stem cell undergoes its transformations, are the subject of two reports. Recent analyses have shown that stem cells can generate cells of a type far removed from the tissues from which the original stem cells were derived. Clarke *et al.* (p. 1660; see the cover and the news story by Vogel) have explored the limits of stem cell multipotentiality. When isolated adult stem cells are given an opportunity to experience a more embryonic environment, either by coculture with embryonic stem cells or by culture within an early embryo, they display even greater developmental diversity than expected. Neuronal stem cells gave rise to

CONTINUED ON PAGE 1547

### HOW A BACTERIUM INVADES AN IMMUNE CELL



The tick-transmitted bacterial infection, human granulocytic ehrlichiosis, is a disease of emerging public health importance, as the same tick also transmits Lyme disease and the two diseases can occur together. Apart from this interest, this is the only bacterial pathogen known to enter and survive within phagocytic cells of the immune system called neutrophils. Herron *et al.* (p. 1653) have discovered a molecular interaction that offers a promising drug and vaccine target for this problematic disease. The bacterium can produce a mimic of a cell-adhesion molecule called P-selectin, which allows the bacterium unimpeded host-cell adhesion and entry. The authors can also cause the bacterium to enter nonhost cells by engineering them to produce a P-selectin receptor.



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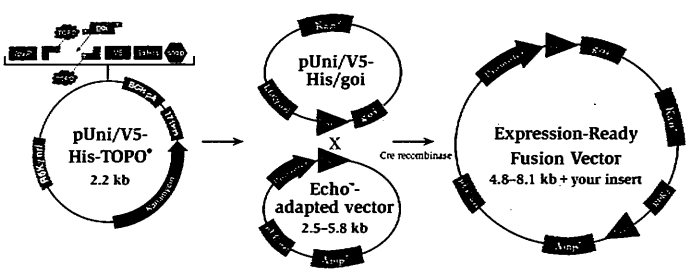


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# THIS WEEK IN *SCIENCE*

CONTINUED FROM PAGE 1545

cells of muscle and liver, as well as some of the outcomes previously seen. Thus adult stem cells may show greater potential, and share greater commonality, than so far thought. Phillips *et al.* (p. 1635) have produced an exhaustive description of the molecular phenotype of a hematopoietic stem cell. Roughly half of the identified transcripts are related to known proteins, and categories of cell signaling, RNA synthesis, and cellular metabolism are well represented. The database offers numerous intriguing expression profiles for further study; the details of their data are presented on an interactive Web site.

### ADDING TO RNA'S REPERTOIRE

The role RNA plays in biology continues to expand—its originally recognized roles in translation now include several enzymatic functions. Peluso *et al.* (p. 1640) now show that the 4.5*S* RNA component of the signal recognition particle (SRP) accelerates both association and dissociation of the guanosine triphosphatases Ffh and FtsY, the protein components of the SRP and the SRP receptor, respectively. Because a part of the RNA is thought to interact directly with signal sequences recognized by SRP, this finding raises the possibility that a consequence of that interaction is regulation of the binding of SRP to its receptor, just as protein-protein interactions mediate allosteric regulation.

### REPLICATION: A ONE-SHOT DEAL

For all organisms, regulating the replication of their genomes is of paramount importance, as any mistakes can have profound and most often deleterious effects. Perhaps the most basic requirement is ensuring that only one new copy of the genome is made in a cell division cycle. Labib *et al.* (p. 1643) show that the six so-called minichromosome maintenance (MCM) proteins of *Saccharomyces cerevisiae* play a central role in preventing runaway copying of the chromosomes. The MCM proteins, in addition to the initiation of replication, turn out to be absolutely critical for the continued synthesis of the new genetic blueprint. Thus, by preventing the reloading of MCM proteins onto DNA during replication, the cell ensures that only one copy of the genome can be completed.

### HOW CHOLESTEROL AIDS MYCOBACTERIAL INVASION

Mycobacteria, including the agent that causes tuberculosis, must invade cells and then multiply in specially adapted vacuoles within the host cell. Gatfield and Pieters (p.1647) examined the mechanism of pathogen invasion and found a surprising requirement for cholesterol in the host macrophage cell membrane for successful mycobactrerial invasion and colonization. Membrane cholesterol accumulates around invading mycobacteria and appears to be important in ensuring the formation of a vacuole that protects the invading organism from intracellular digestion by the host cell.

### YOU CAN KEEP YOUR IRON

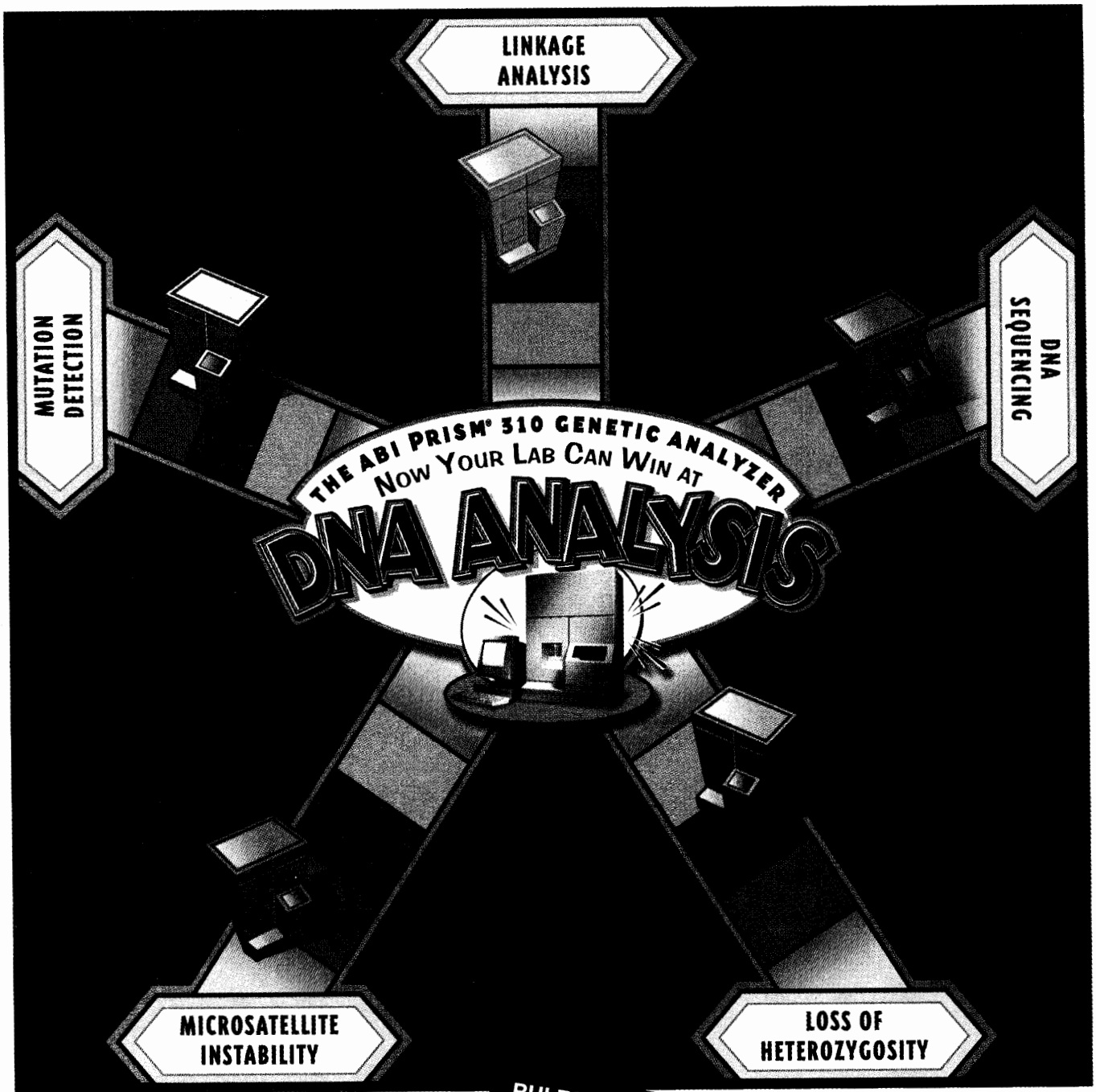
Iron is an essential nutrient for most microbes and pathogens. Posey and Gherardini (p. 1651) looked at the iron requirements of the spirochete responsible for Lyme disease, *Borrelia burgdorferi*, and discovered that the organism lacks any iron-containing proteins. Instead of iron, the metalloenzyme systems of the microbe appear to utilize manganese. Thus, this human pathogen can circumvent one of the host's natural defense systems—the severe lack of free iron in the host environment.

### DEMARCATING COGNITION

In comparison to sensory and motor modalities, cognition uses more anterior portions of the human brain. These areas also are less well defined than the sensory and motor cortices in terms of subserving distinct functional duties, partly because cognitive tasks tend to involve multiple abilities and partly because it has been difficult to design tasks to separate these abilities. Rowe *et al.* (p. 1656) designed a task that separated the maintenance of items in working memory and the selection from among those items for response. They were able to associate area 46 of the dorsolateral prefrontal cortex with the selection phase and area 8 with the maintenance function.

### QUANTIFYING PROTEIN SOFTNESS

Proteins offer a striking illustration of how a collection of weak interactions (hydrogen bonds, salt bridges, and van der Waals forces) support precise three-dimensional structures, as assessed by x-ray crystallography, while providing sufficient flexibility for enzyme catalysis and conformational changes. Zaccai (p. 1604) reviews recent developments in the use of neutron scattering to measure the resilience of two proteins, myoglobin and bacteriorhodopsin, under a variety of conditions and environments. Neutron scattering has the advantage of not needing crystalline samples and can be combined with specific deuteration to spotlight particular regions of a protein.




**RULES OF THE GAME**

**Object:** To sequence, size, and quantitate nucleic acids using any application you choose.

**Requirements:** Selected path must be affordable, convenient, easy to use, versatile, and quick.

**How to play:** Select a genetic analysis method. Analyze nucleic acids. Review results.

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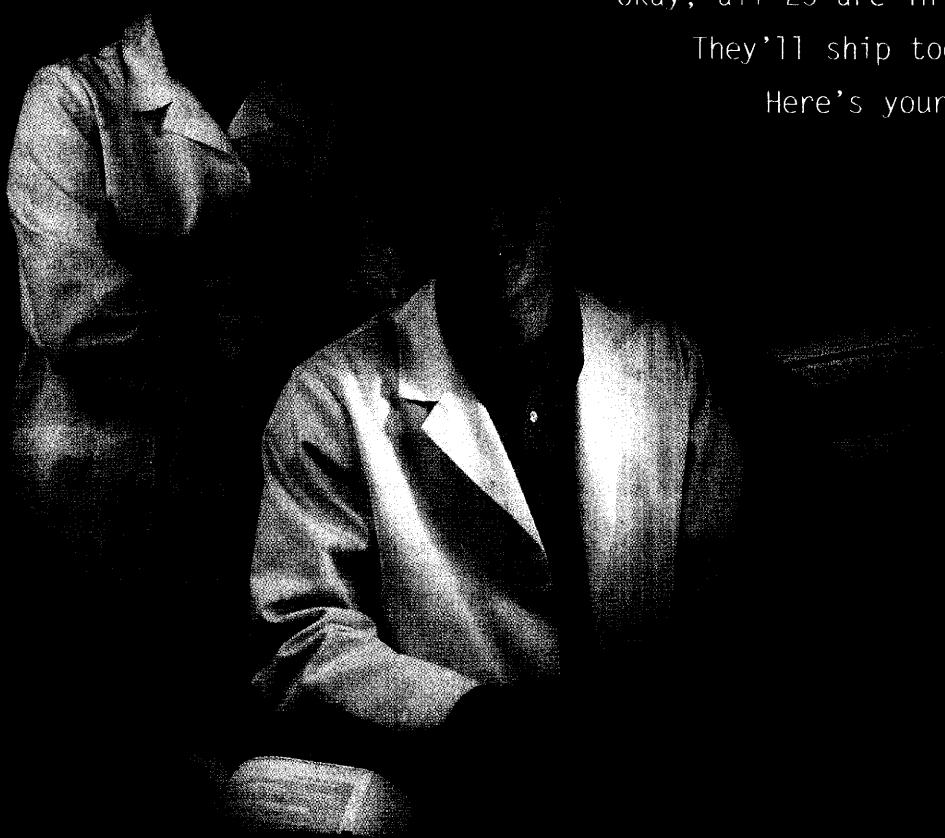


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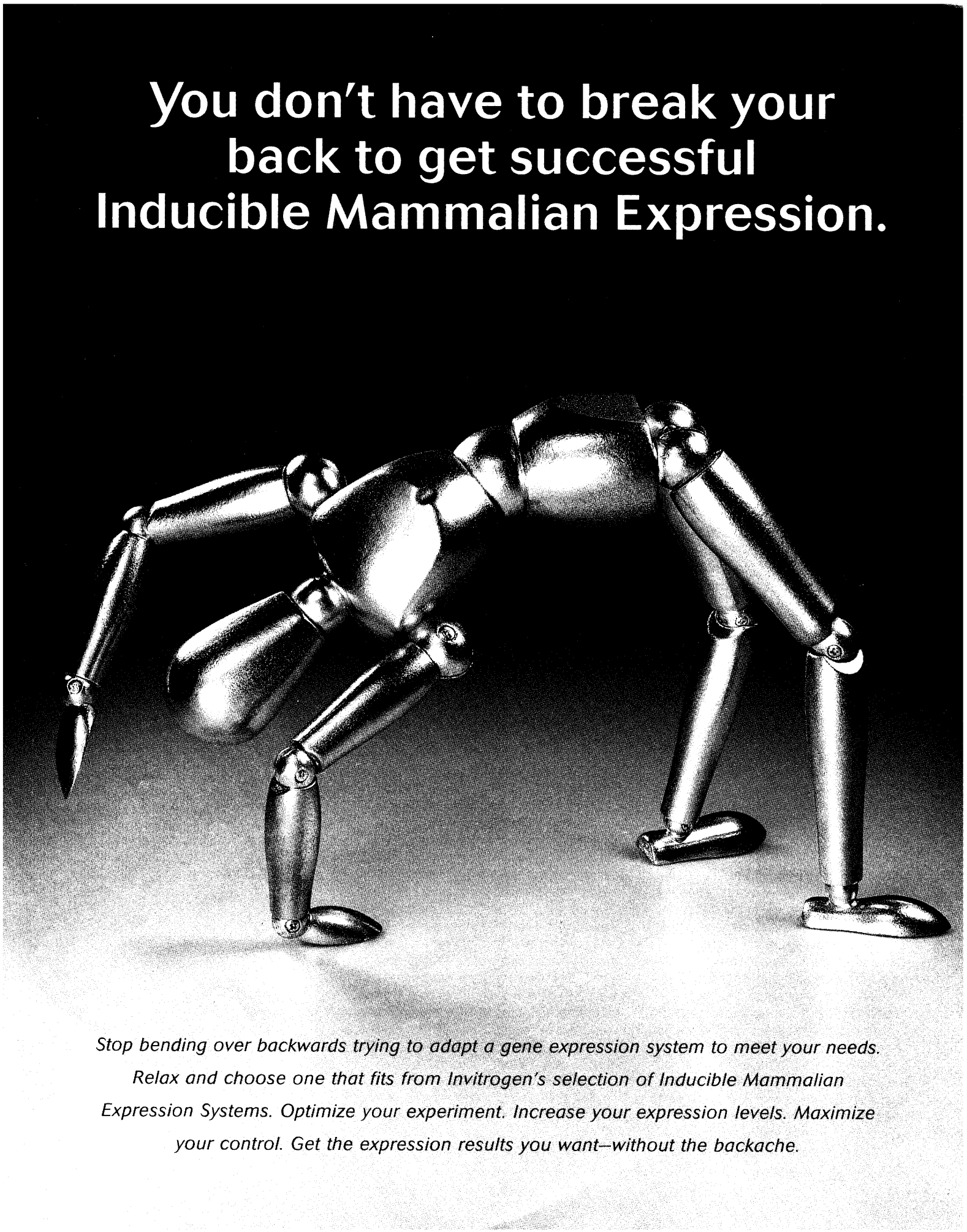
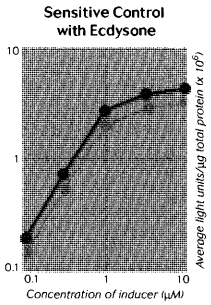
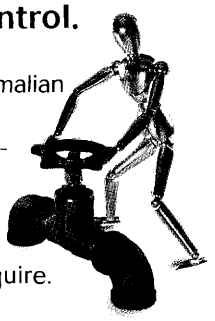


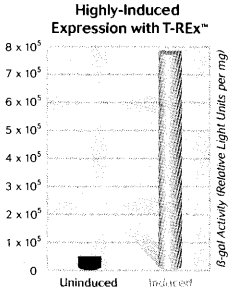
*Stop bending over backwards trying to adapt a gene expression system to meet your needs. Relax and choose one that fits from Invitrogen's selection of Inducible Mammalian Expression Systems. Optimize your experiment. Increase your expression levels. Maximize your control. Get the expression results you want—without the backache.*




## The Ecdysone-Inducible System gives you precise control.



Based on a unique insect regulatory mechanism, the Ecdysone-Inducible Mammalian Expression System allows you to easily and efficiently modulate protein production levels. With the Ecdysone System you can perform time- or dosage-dependent inducible expression studies and get the precise results you require.

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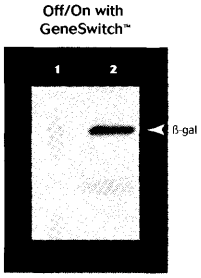
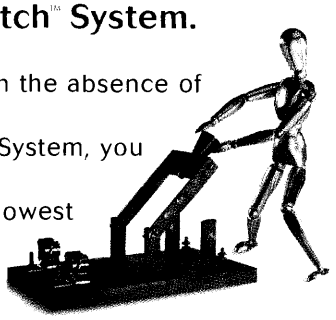



## For the lowest basal levels, get the GeneSwitch™ System.



GeneSwitch™ uses a promoter that is transcriptionally silent in the absence of inducer. With the extremely tight control of the GeneSwitch™ System, you can express even the most toxic proteins. For the absolute lowest basal expression levels, you need the GeneSwitch™ System.

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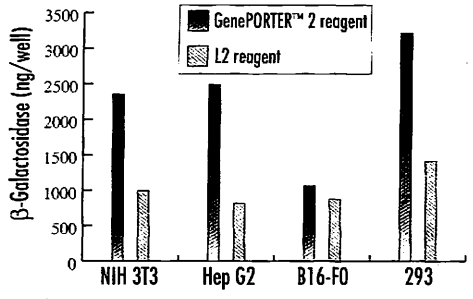


A β-gal expression plasmid was delivered into cells in 24-well plates with either GenePORTER 2 reagent or a competitor's transfection reagent (L2). Each reagent was used according to the manufacturer's protocol. Following transfections (48 hours), β-galactosidase was measured by colorimetric assay with the Enhanced b-Galactosidase Assay kit (GTS Cat =A10100K).

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## Transfected Cell Types

| | |
|---|---|
| 293 | Murine Es cells |
| Jurkat | MM54.Sp/Thy |
| NIH 3T3 | AKR-2B |
| B16-F0 | MIN6 |
| PC-12 | Hepa-1clc7 |
| BHK-21 | Primary hepatocytes |
| CHO-K1 | NSC34 |
| DDT1 MF-2 | D6P2T |
| CV-1 | C6 |
| COS-1 | INS-1 |
| COS-7 | PEF |
| MO 7E | RK 13 |
| FL5.12 | PERN |
| MCF7 | Primary keratinocyte |
| K-562 | SL-29 |
| KG-1 | Primary embryonic fibroblast |
| CL-01 | MDBK (NBL-1) |
| HMSC | A6 |
| HeLa | HEQ 3-3 |
| HeLa S3 | CFT-1 |
| SW 1353 | Chicken cardiomyocyte |
| MRC-5 | RP-19 |
| FaDu | Y-79 |
| LNCaP.FGC | T-84 |
| PC-3 | $C_2C_{12}$ |
| U-87 MG | BC 3H1 |
| PM-RCC | BALB-10 |
| Hep 3B | Bovine endothedial |
| Hep G2 | T-89G |
| HEC-1 | JAR |
| LoVo | SKOV-3 |
| U937 | Equine derma |
| 293T | L-929 |
| 911 | EKER |
| NTD-1 | SW-1353 |
| 10T 1/2 | H-292 |
| Huh7 | Rat cortical neurons |
| 293EBNA | |
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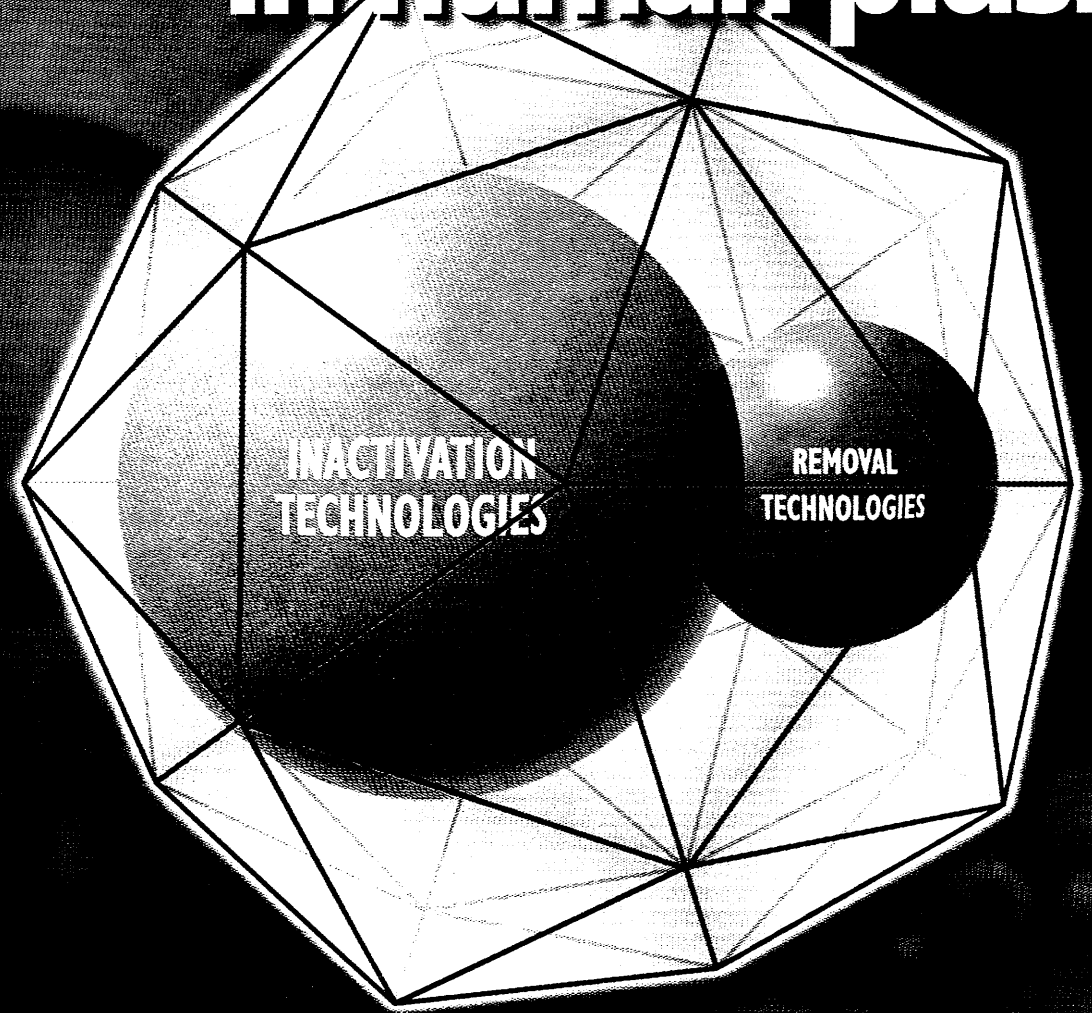


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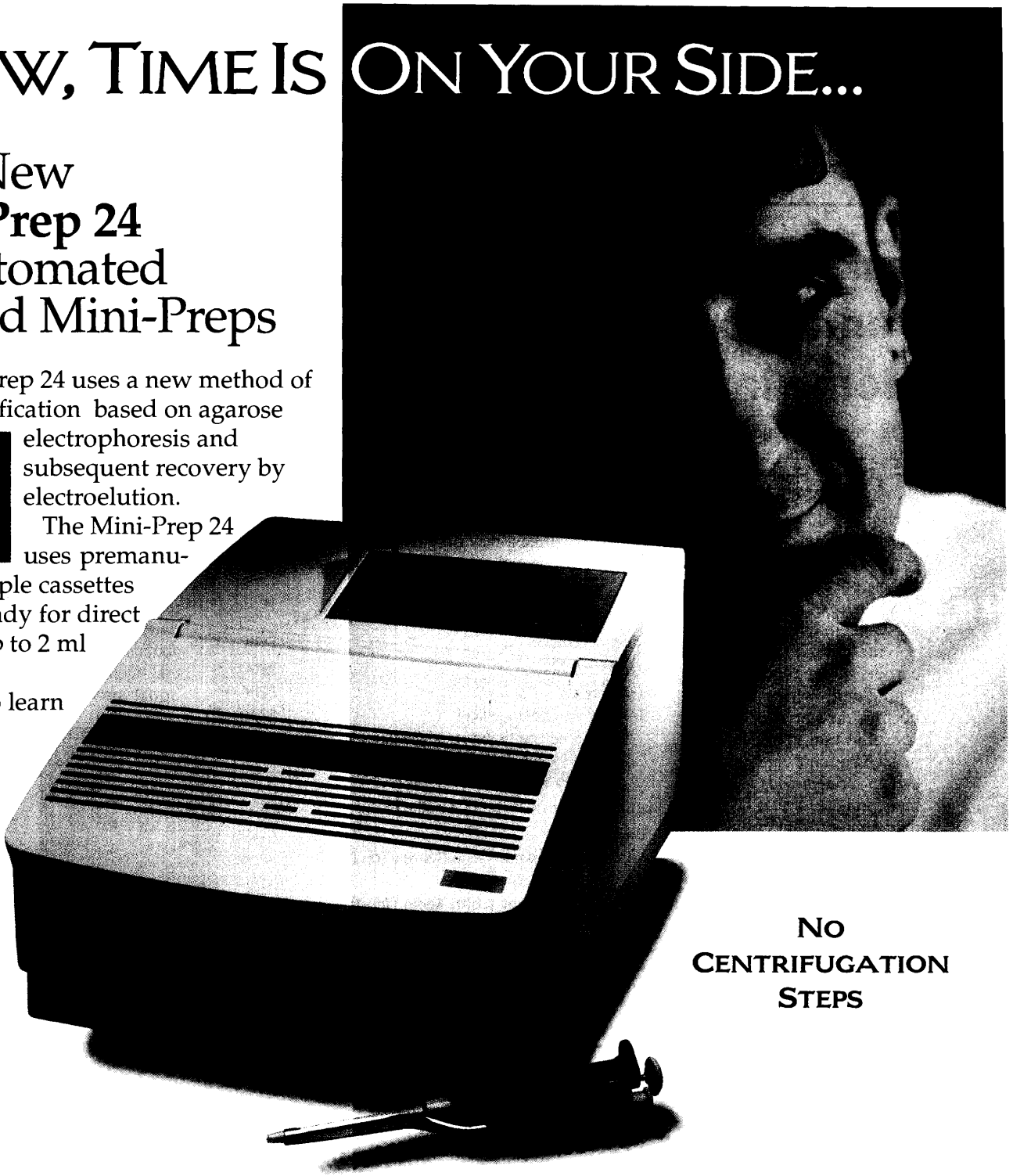

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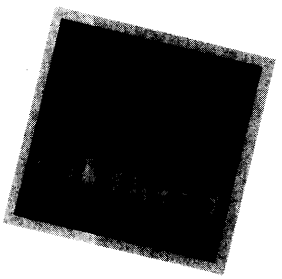

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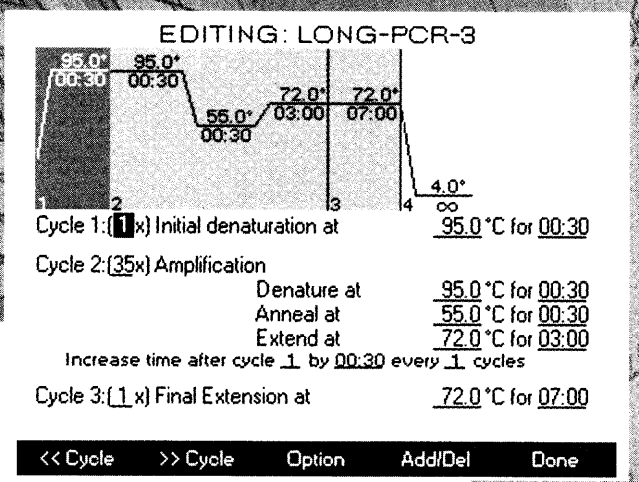


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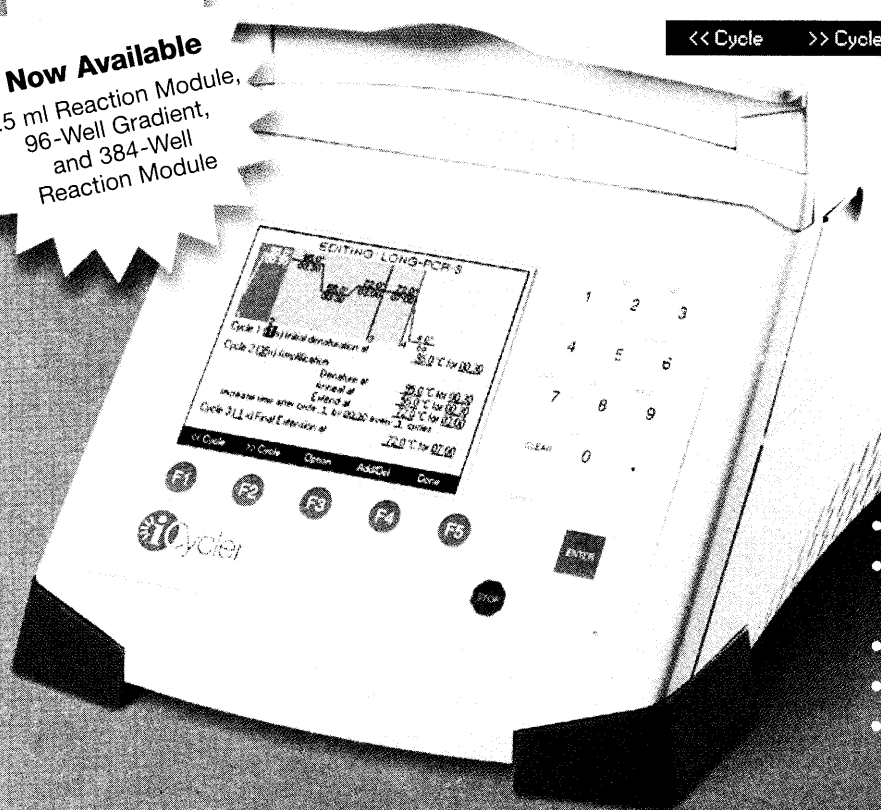

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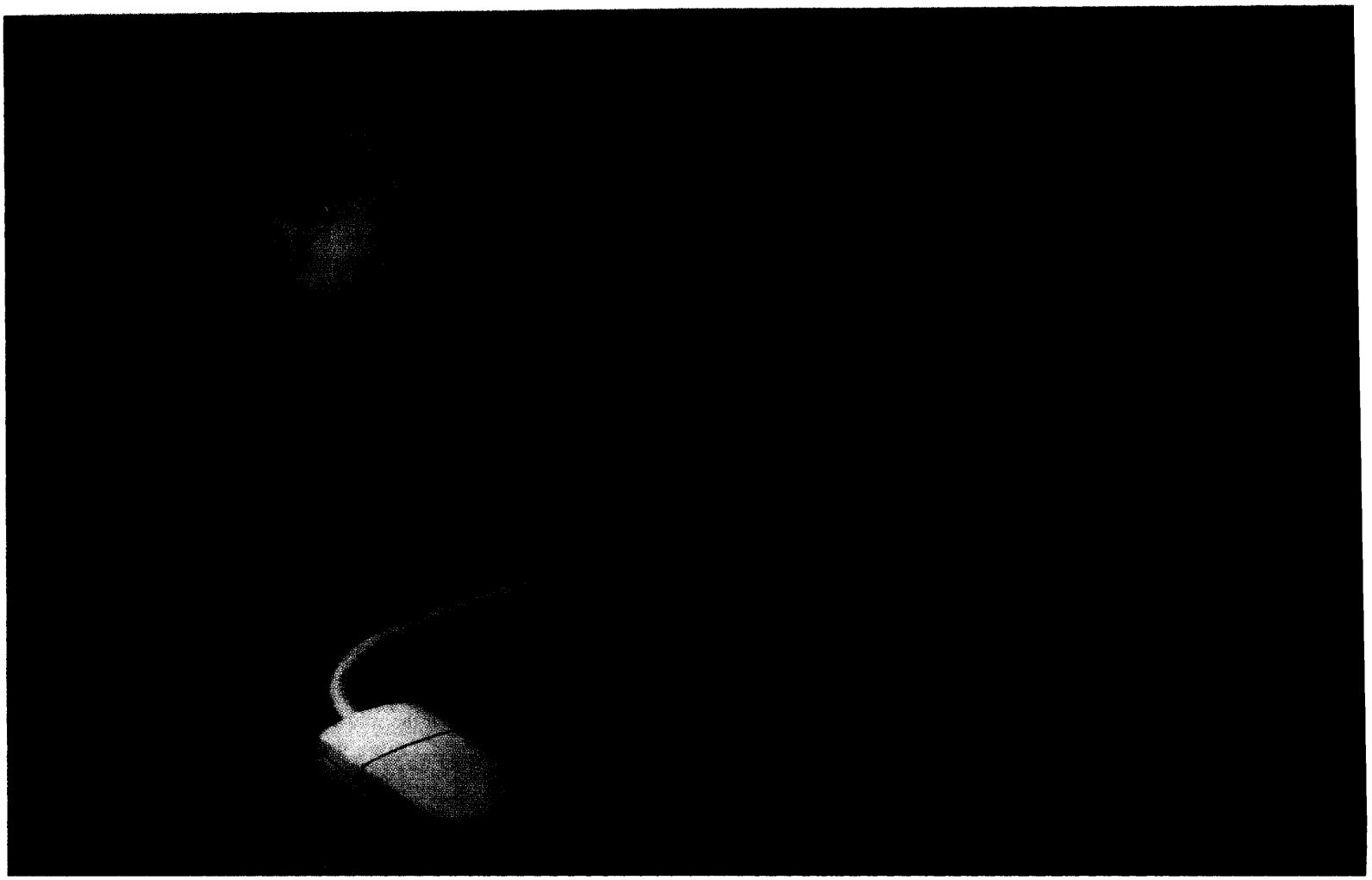

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TaKaRa

# The Taming The Shrew

## First Quiet, Then Command

## Takara's Novel Adenovirus Cre/loxP Kit

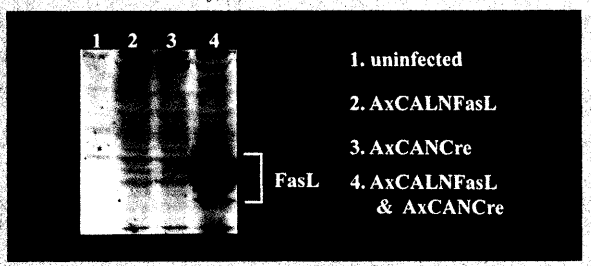
Provides a Convenient Cre-mediated ON/OFF Switching System*1 to Control Cytotoxic Gene Expression in Cultured Mammalian Cells and Animals

### An example of the Utility of This System

**Generation of Recombinant Adenovirus Expressing rat Fas-ligand** successfully achieved using a Cre-*lox*P recombination system in the 293 cells which are susceptible to Fas-mediated apoptosis.

**Fas Ligand Expression in COS-7 Cells detected by Western Blotting** with an anti-human Fas-ligand antibody. The cells co-infected with AxCALNFasL and AxCANCre ("ON" expression) expressed Fas-ligand, while the cells infected with AxCALNFasL ("OFF" expression) alone did not express detectable levels of rat Fas-ligand.

*Courtesy of Dr. T. Okuyama, Department of Genetics, National Children's Medical Research Center, Tokyo*




### Adenovirus Cre/loxP Kit

(Code # 6151; for 5 recombinants)

Convenient system of the recombinase-mediated switching for gene expression in mammalian cells: In the cassette cosmid, pAxCALNFLw, a stuffer DNA is placed between the potent CAG promoter and the insert cDNA at a unique *Swa*I site. Its excisional deletion with Cre recombinase triggers a many fold increase in expression of the gene encoded by the downstream sequence under the control of CAG promoter ("ON" expression).

### Adenovirus Expression Vector Kit

(Code # 6150; for 5 recombinants)

High titer recombinant adenoviruses can be easily and efficiently obtained using the COS-TPC method*2: A recombinant adenovirus is generated through homologous recombination of cassette cosmid with digested DNA-terminal protein complex of Adenovirus in the producer cell, 293.

References 1. *1 Kanegae, Y. et al. (1995) *Nucl. Acids Res.* 23, 3816
2. *2 Miyake, S. et al. (1996) *Proc. Natl. Acad. Sci. USA* 93, 1320
3. Okuyama, T. et al. (1998) *Gene Therapy* 5, 1047
4. Sudo, M. et al. (1999) *Mol. Brain Res.* 65, 176



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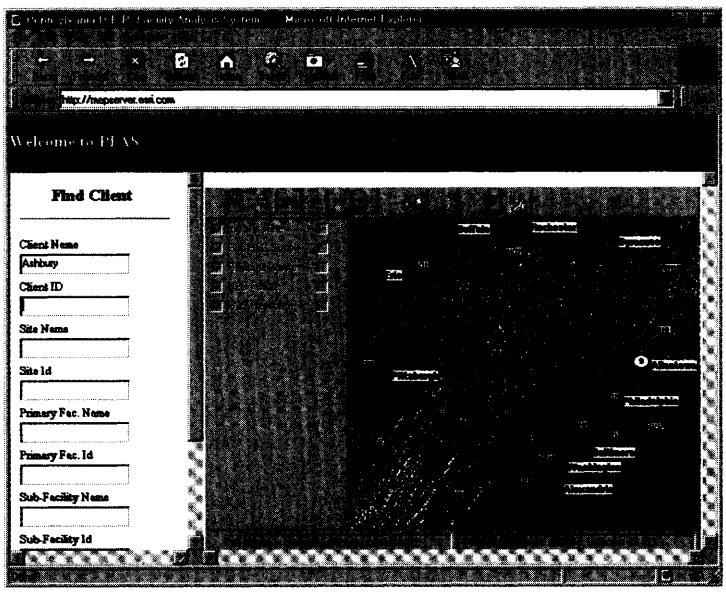


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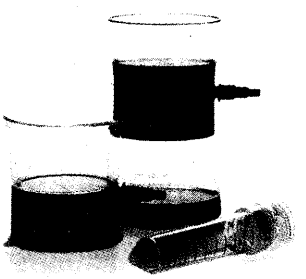

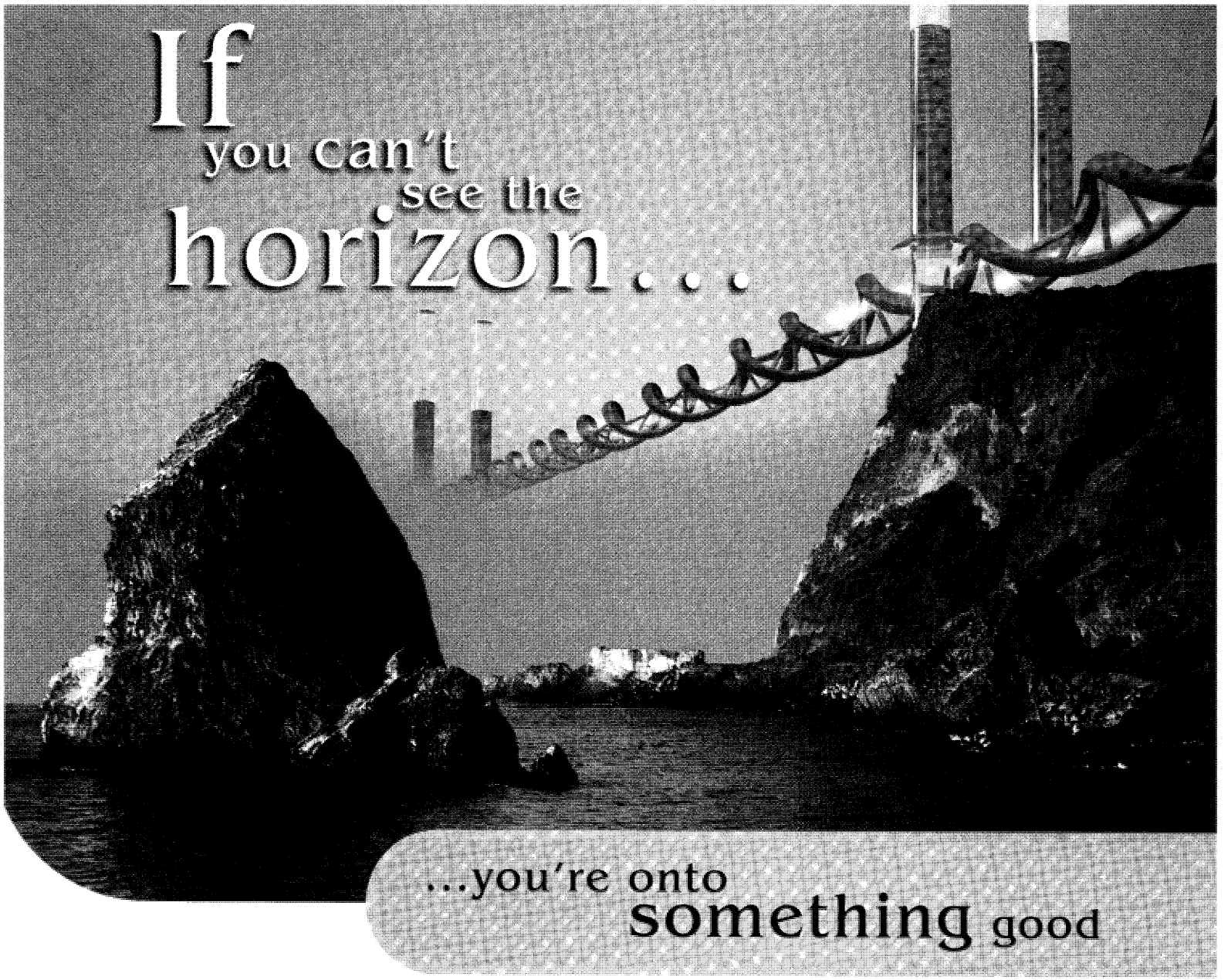


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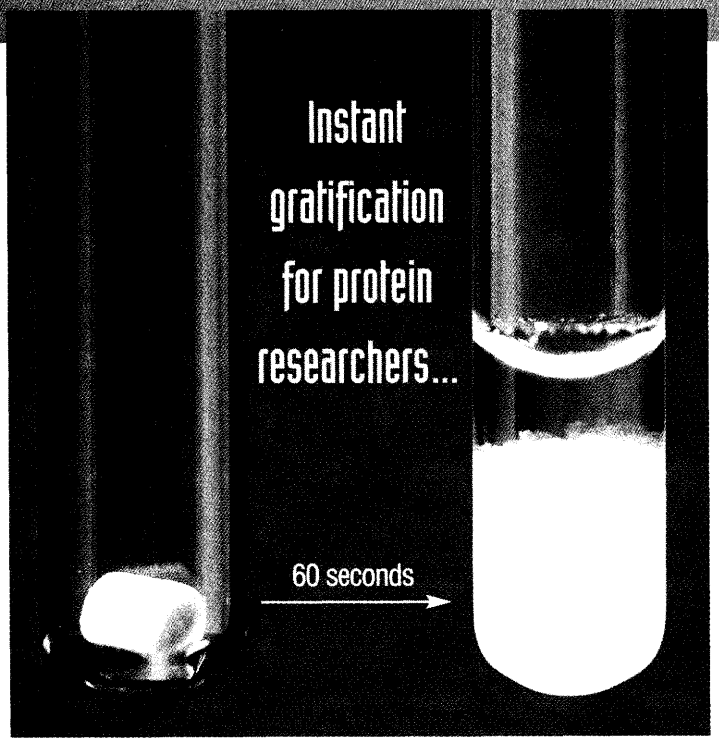
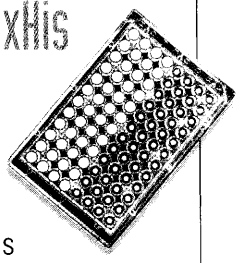



# SwellGel™ Nickel Chelating Discs for purification with the 6xHis tag reconstitute in just 60 seconds!



The new SwellGel™ 96-Well System is an instant platform for high-capacity and high-throughput fusion protein purification.

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- Higher throughput format binds more than 1 mg of green fluorescent protein per well
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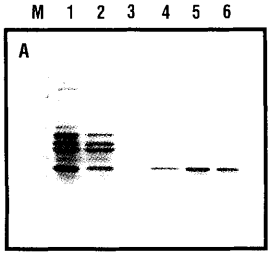
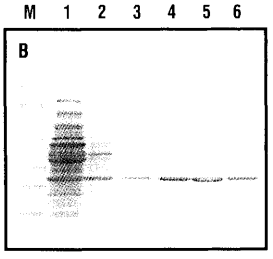
- Works as well as traditional wet nickel-chelated agarose gels ... but without the hassles
- Excellent stability and room temperature storage – no need to refrigerate




**SwellGel™ Nickel Chelating Discs provide excellent binding capacity.** Recombinant 6xHis-tagged green fluorescent protein (GFP) expressed in a 250 ml *Escherichia coli* BL $_{21}$ cell culture was extracted by adding 5 ml of B-PER™ II Bacterial Protein Extraction Reagent (Pierce # 78260). After removing the cellular debris, 100 µl of the lysate was loaded into the wells of a filter plate containing either SwellGel™ Nickel Chelating Discs or regular nickel-chelated agarose. The unbound proteins were removed by low speed centrifugation (500 *g* for 3 minutes) and washed twice with 250 µl of phosphate buffer (50 mM $Na_3PO_4$, 300 mM NaCl, 80 mM imidazole, pH 7.6). The bound 6xHis-tagged GFP was eluted three times with 100 µl of elution buffer (50 mM $Na_3PO_4$, 300 mM NaCl, 250 mM imidazole, pH 7.6). Samples from each step were collected for SDS-PAGE analysis using 4%-20% gradient gels. Panels **[A]:** SwellGel™ Nickel Chelating Discs rehydrated in 100 µl of sample solution; **[B]:** regular nickel-chelated agarose loaded with 100 µl of the sample after equilibration buffer was removed from the resin.
**Lanes: M**: Blue Ranger™ Molecular Weight Marker; **1:** Flow-through; **2-3:** Washes; **4-6:** Elutions

## Ordering Information

| Product # | Description | Pkg. Size |
|---|---|---|
| **20147** | SwellGel™ Nickel Chelating Discs,* Kit | Kit |
| | Includes: 96-Well Purification Filter Plate | 1 |
| | SwellGel™ Nickel Chelating Discs | 96 |
| | 96-Well collection plate | 1 |
| | Start Buffer | 20 ml |
| | 4M Imidazole solution | 12 ml |
| **75824** | SwellGel™ Nickel Chelating Discs,* 96-Well Filter Plate | each |
| | Includes: 96-Well Purification Filter Plate | 1 |
| | SwellGel™ Nickel Chelating Discs | 96 |
| | 96-Well Collection Plate | 1 |

**Patent Pending*

**For more information or to download an instruction booklet for this product, visit the Pierce web site at *www.piercenet.com***

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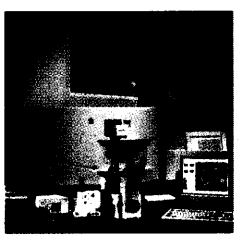

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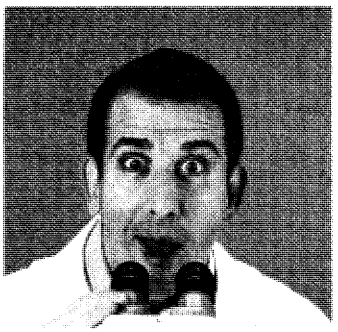

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