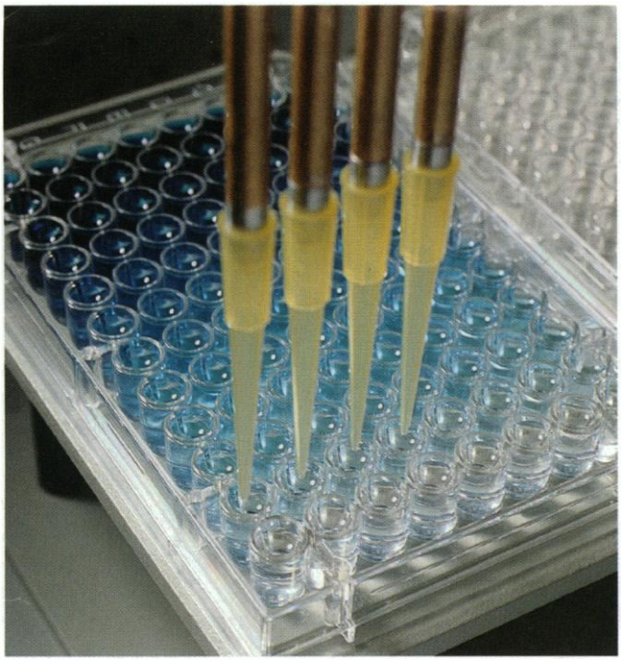
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

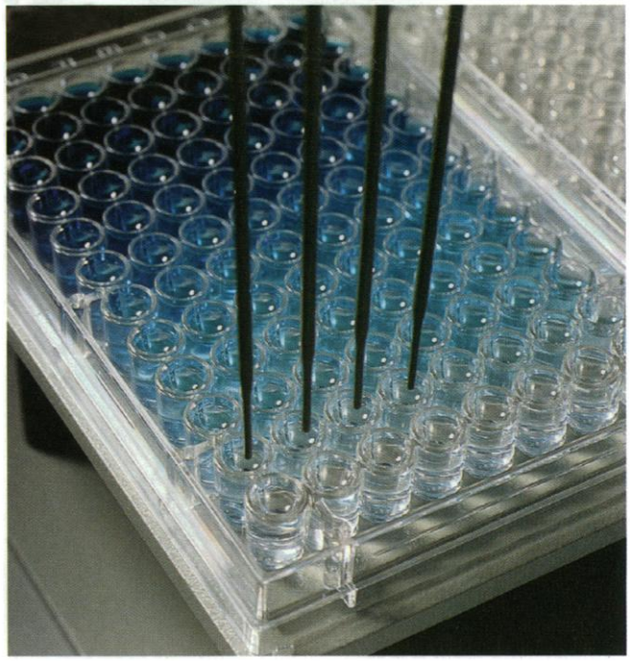
# SCIENCE

28 OCTOBER 1994 $6.00
VOL. 266 • PAGES 513–700

## *development*

FRONTIERS IN BIOLOGY





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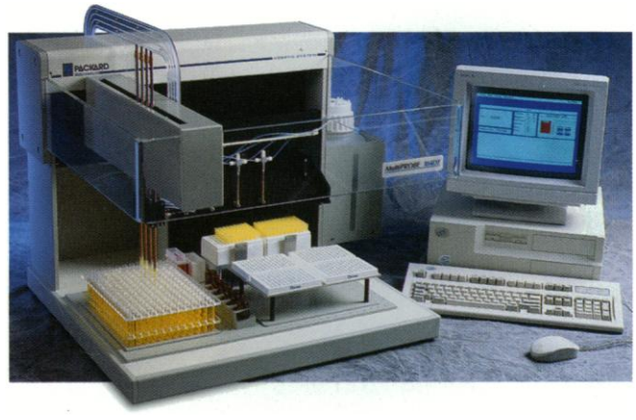

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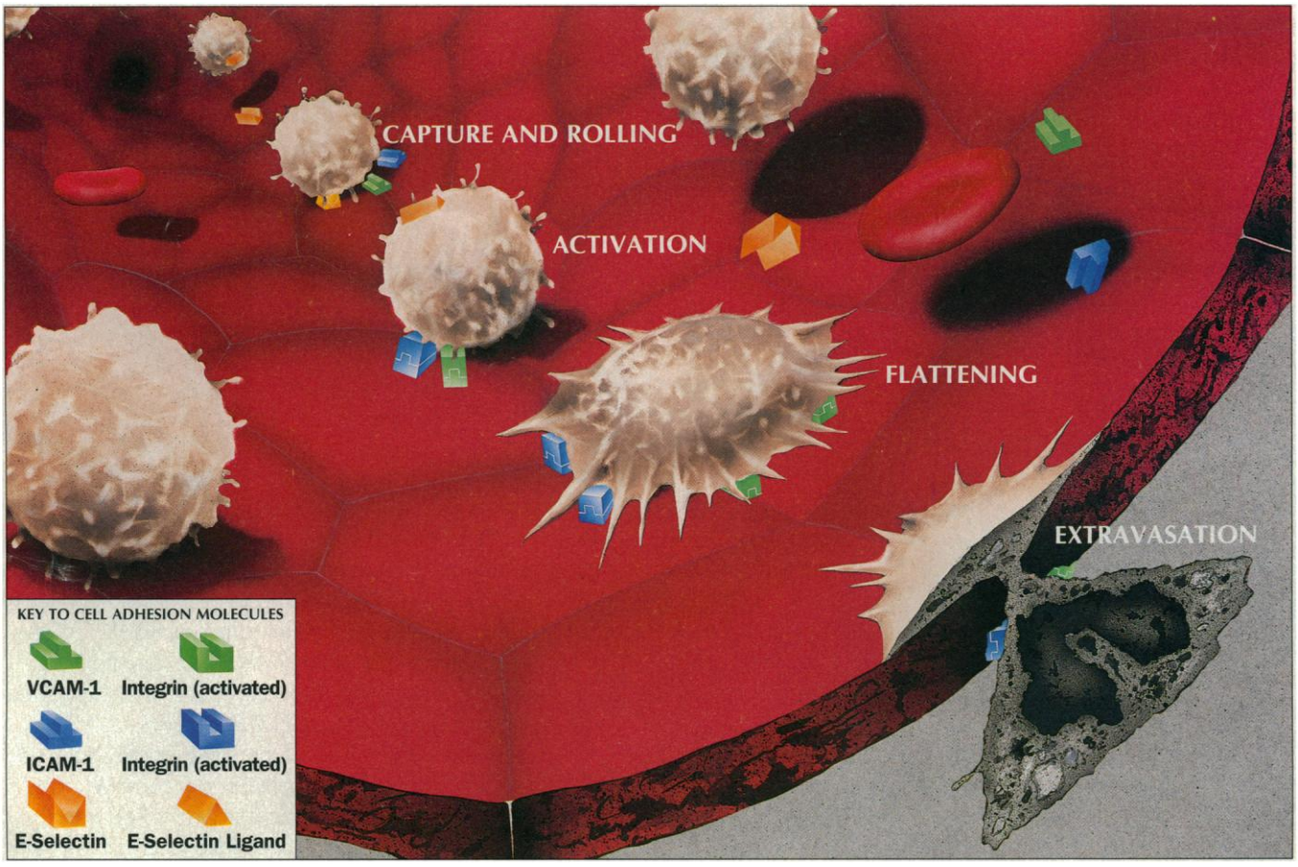


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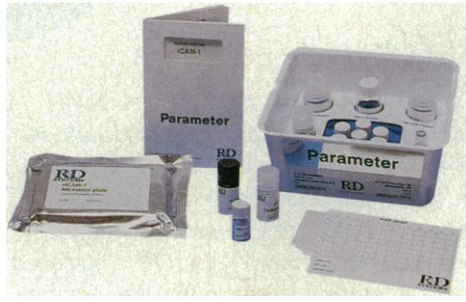



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Remember the milestones in your life. The ones that revealed your talent to create, solve, explore, and discover.

Maybe it was a special science fair project. Or a certain insight you had in a college lab. Or maybe it was a tool, like an EM, that let you really delve into what makes things tick. Somehow it all came together into a career in the sciences.

Biosearch specializes in creating tools that fuel your inner drive to discover. Tools that allow your imagination to take on today's frontiers.

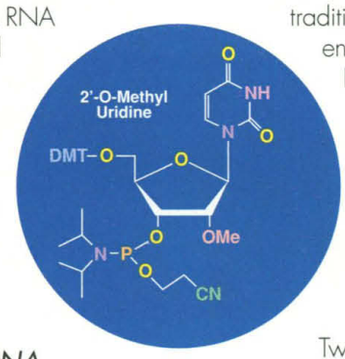
## *RNA*

RNA oligomers have shown promise in therapeutic and diagnostic applications, including inhibition of viral replication, cancer etiology, and gene regulation and expression.

To bring these applications within easy reach, Biosearch was the first to introduce a complete, automated RNA synthesis system with nucleotide monomers, reaction columns, pre-packaged reagents, and optimized synthesis protocols.

Our new Expedite™ RNA chemistry makes your work-up procedures faster, easier, and more efficient. The milder cleavage and deprotection conditions reduce chain degradation and increase yield. The Expedite RNA reagents employ our patented betacyanoethyl phosphoramidite chemistry that's become the method of choice in DNA and RNA synthesis.

Our researchers are currently developing protocols for large-scale synthesis of RNA oligomers. (Photo of RNA crystal, courtesy of Dr. Alex Rich, MIT, was synthesized at a scale of 70 µ mole on Biosearch's 8800 Synthesis System.)



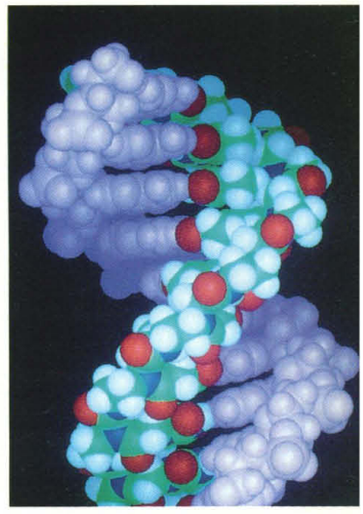

## *Therapeutic and diagnostic grade DNA*

Researchers in the clinical and diagnostic use of DNA are on the verge of creating a new class of pharmaceuticals. Biosearch is proud to pioneer new tools for their work.

Biosearch is the world's leading supplier of systems, chemicals, and reagents for the synthesis, purification, and analysis of therapeutic and diagnostic DNA. We've tightened the specifications on our products to ensure that they can be used for the most demanding applications. A Certificate of Analysis is automatically supplied with all of our DNA synthesis reagents.

We've also substantially expanded our manufacturing capacity to meet the needs for large single-batch production of material, minimizing your need for internal quality control.

In addition to standard reagents, Biosearch can also supply phosphoramidites and bulk quantities of synthesized oligomers on a custom-synthesis basis.



## *PNA*

Peptide Nucleic Acids–PNA oligomers. These molecules are so novel that they're rewriting the very nature of nature. Biosearch is the world leader in the development and synthesis of these exciting new molecules.

Similar to DNA and RNA, PNA carries information in sequences of the four bases: adenine, guanine, cytosine, and thymine. In PNA, however, these code carriers are connected to a completely different backbone–a polyamide backbone similar to that found in peptides. PNA oligomers are more stable than their natural counterparts yet bind more specifically and with higher affinity to natural DNA and RNA.

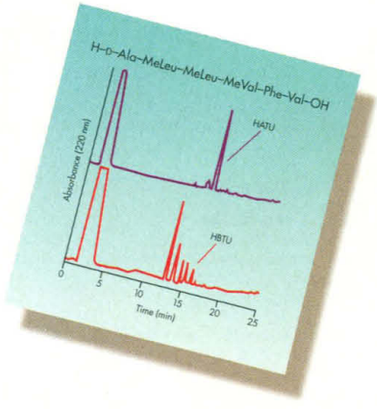
PNAs can be used in many of the same applications as traditional DNA. Their greatest contribution, however, may come from applications that can't be performed using traditional DNA oligonucleotides, such as restriction enzyme blocking, PCR clamping, and DNA mapping.

Biosearch can provide you with custom PNA oligomers, or the monomers, supports, and reagents to synthesize your own oligomers.

## *HOAt and HATU peptide coupling reagents*

Two new coupling reagents, HOAt and HATU, simplify your peptide synthesis. These new reagents enhance coupling yields and reduce racemization and coupling times. They are particularly effective with difficult couplings and in the synthesis of peptides containing hindered amino acids.

HOAt and HATU have structures similar to the commonly used reagents HOBt and HBTU, and are compatible with all standard activation strategies.



# Keep Up With Your Imagination.

### *PEG-PS™ peptide synthesis supports*

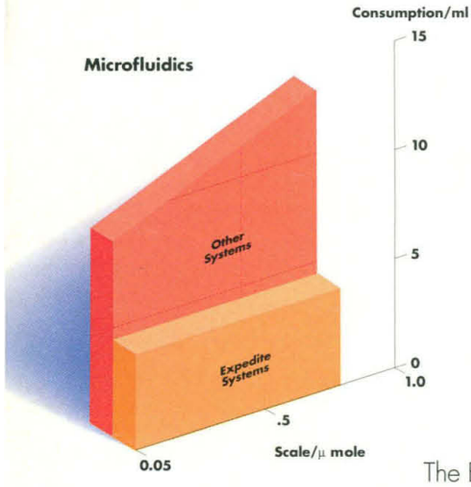
PEG-PS (polyethylene glycol-polystyrene) peptide synthesis supports from Biosearch help you achieve improved peptide purity with shorter cycle times.

Unlike traditional supports, PEG-PS beads more closely resemble the nature of the growing peptide chains. Solvation of the peptide resin is higher, resulting in a higher peptide purity. Synthesis is fast and effective due to high coupling efficiency and minimal side reactions.

PEG-PS supports are easy to handle, compatible with a wide range of solvents, and are especially well suited for the synthesis of long or difficult peptides.

### *Microfluidics*

In the real world, achieving "end product" is not the only concern. There are dozens of production costs as well as the escalating costs of hazardous waste disposal.




Biosearch's Expedite Nucleic Acid Synthesis System, with its patented microfluidics technology, not only enables fast cycle times but also provides the bonus of reduced reagent consumption. The distance between the reagent reservoir and the column is minimized so that a single coupling cycle requires less than 4.5ml of reagents. The Expedite system (with optional trityl monitor) can also separate the chlorinated waste–simplifying disposal tasks and reducing associated costs.

### *Membrane synthesis*

Perform nucleic acid synthesis on a membrane? It's now possible–and practical–thanks to Biosearch Nucleic Acid Membrane Supports, a breakthrough synthesis technology developed by Biosearch.

Biosearch membrane supports use a proven PTFE membrane system that directly replaces traditional controlled pore glass (CPG) supports. Membrane devices have standard luer fittings, so they can be plugged into any brand of synthesizer.

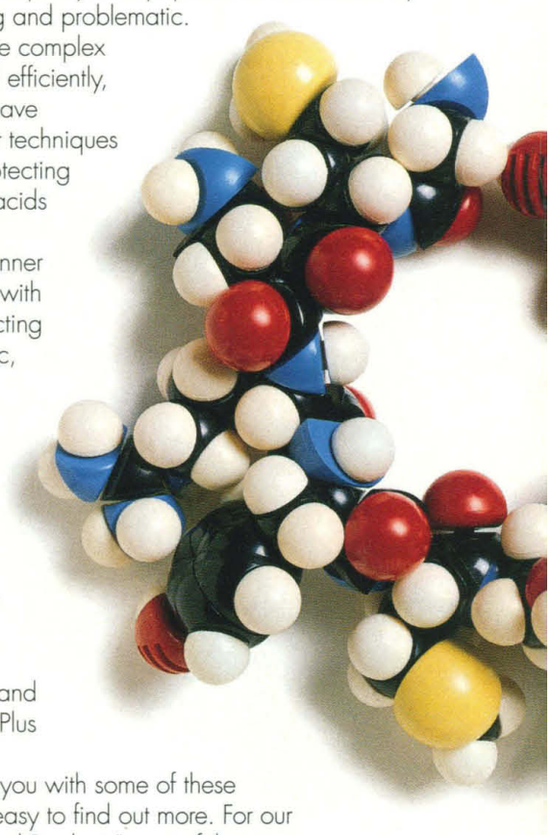
Biosearch membrane supports allow you to synthesize both long and short oligomers on the same type of membrane; no longer do you need to select the size of the CPG according to the length of the oligomer.

With Biosearch membrane supports, not only do you eliminate beads, but there's no centrifuging and no washing. Just remove the membrane from its holder, cleave, and deprotect.

### *Allyl-based protection for complex peptides*

The synthesis of cyclic, branched chain, sulfonated, glycosylated, and phosphorylated peptides have traditionally been time consuming and problematic.

To synthesize these complex peptides quickly and efficiently, Biosearch scientists have perfected convenient techniques using allyl-based protecting groups. Allyl amino acids can be selectively deprotected in a manner which is compatible with other classical protecting groups (such as Fmoc, Boc, *t*Bu), sensitive amino acids (Met, Trp), and side chain modifications (Tyr($SO_3H$)). Biosearch has also developed protocols for the fully automated synthesis of cyclic peptides, branched peptides, and MAPs on our 9050 Plus PepSynthesizer.™



If we've intrigued you with some of these innovative tools, it's easy to find out more. For our "Directory of Chemical Products"–one of the most comprehensive synthesis tool kits in the world–call the Biosearch Group in the US and Canada at 1-800-872-0071, in Germany at (49) 040-853267-36, in Japan at (03) 3471-8191, in France at (33) 1 30127002, and in the UK and the rest of Europe at (44) 0923 211107.

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ISSN 0036-8075
28 OCTOBER 1994
VOLUME 266
NUMBER 5185

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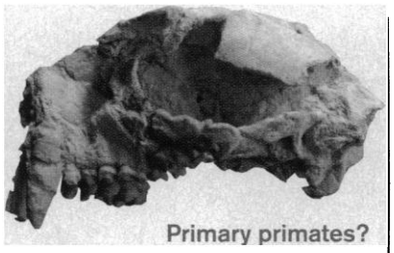
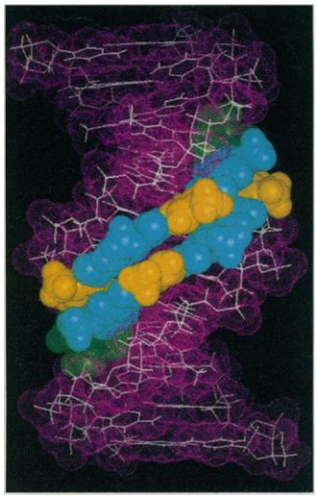


Primary primates?

**541**

**646**
**Specificity reversed at last**



## NEWS & COMMENT



## RESEARCH NEWS



## RESEARCH ARTICLE



## REPORTS



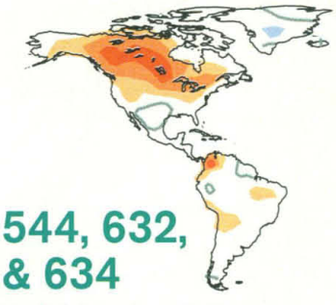
## DEPARTMENTS

COVER

Nomarski image of the grasshopper central nervous system and adjacent body wall showing the distribution of Engrailed (black) and Even-skipped (brown) proteins. The neural expression patterns of these genes are well conserved in insects, but variations in their earlier patterns of expression during segmentation highlight some of the potential differences in early patterning mechanisms among various insects. See page 581. [Image: Nipam Patel, using a Zeiss ProgRes 3012 digital camera]


## Frontiers in Biology: Development





**544, 632, & 634**

Explaining decade-long climate change



◩ Indicates accompanying feature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Domestic individual membership and subscription (51 issues): $92 ($50 allocated to subscription). Domestic institutional subscription (51 issues): $215. Foreign postage extra: Mexico, Caribbean (surface mail) $50; other countries (air assist delivery) $95. First class, airmail, student and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. **Printed in the U.S.A.**

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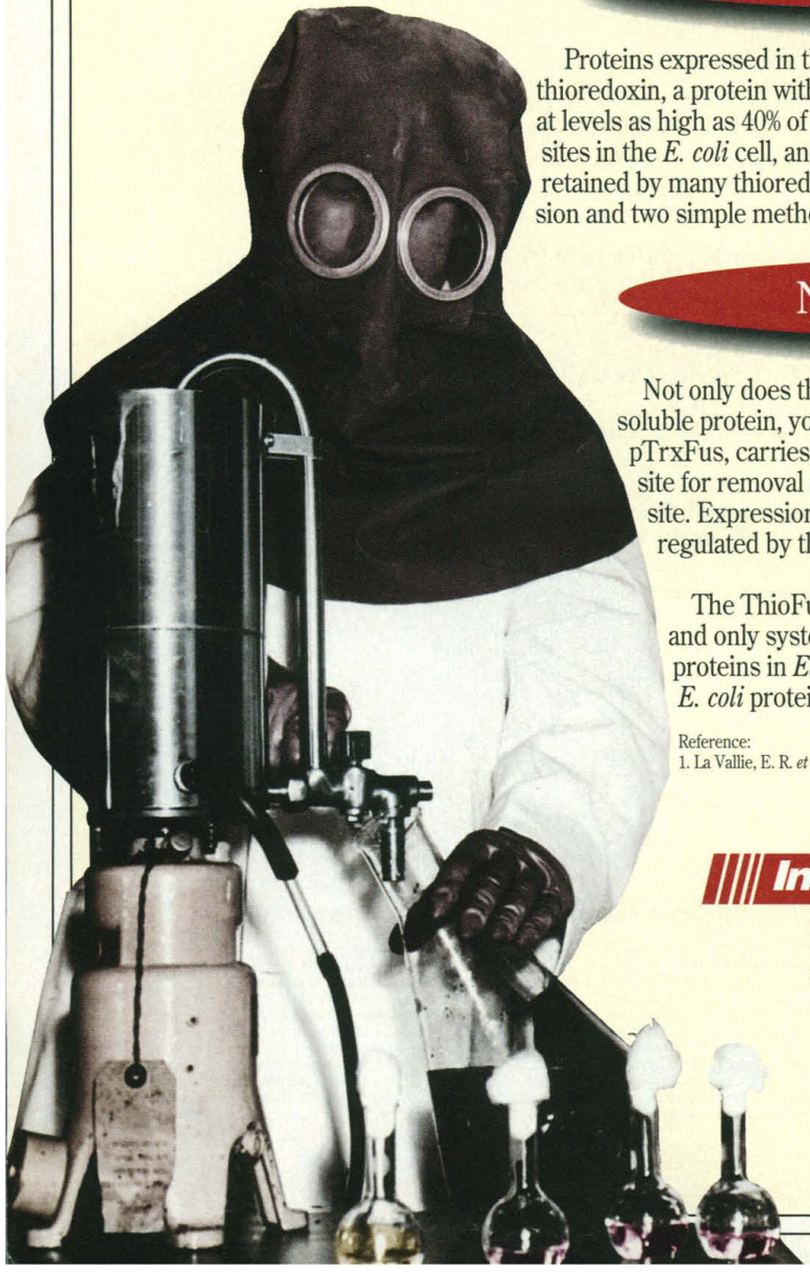

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Reference:
1. La Vallie, E. R. *et al.* (1993) *Bio/Technology* **11**: 187-193.



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edited by PHIL SZUROMI

### Heme coherence

Bond-breaking events such as photolysis can excite vibrational modes in the resulting product states. In ligand dissociation from heme proteins, it has been thought that low-frequency heme modes would be rapidly overdamped by the presence of the surrounding protein. Femtosecond laser spectroscopy studies by Zhu *et al.* (p. 629) reveal two low-frequency modes corresponding to heme doming and iron-histidine motion that persist after the photodissociation of nitric oxide (NO) from myoglobin (Mb). This coherent motion appears to arise from the change in electronic forces as the system crosses over from the MbNO excited-state potential to the Mb ground state.

### Pacific effects

Records of temperature and precipitation over the Pacific Ocean and North America seem to have varied in roughly decadal cycles; the 1980s were particularly warm, leading to suggestions of a recognizable signal of greenhouse warming. Two studies comparing simulations to climate records, Kumar *et al.* (p. 632) and Latif and Barnett (p. 634) (see the related news story by Kerr, p. 544) conclude that these decadal climate patterns likely arise from effects of sea surface temperatures in the Pacific Ocean (which probably result from natural patterns) on atmospheric circulation.

### Embryos of old

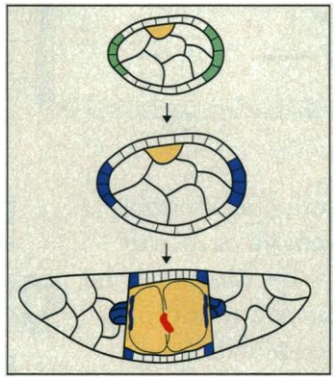
Fossils of the embryonic stage of animals, particularly from when animal life exploded in the Cambrian, are scarce. Zhang and Pratt (p. 637) describe several embryos, including some that appear to contain blastomeres, from rocks in China that are about 510 million years old. The embryos are apparently of arthropod affinity and may be of trilobites also found in the rocks.

### A mixed approach to DNA binding

The Skn-1 protein of *Caenorhabditis elegans* is a maternally produced product that is required for the proper specification of intestinal, muscle, and pharyngeal cell fates in the early embryo. Embryos mutant for *skn-1* overproduce hypodermal (skin) cells. The Skn-1 protein contains a basic region to that in the basic leucine zipper (bZIP) transcription factors, but has no leucine zipper region that would dimerize for DNA binding. Blackwell *et al.* (p. 621) characterized the DNA binding of Skn-1 and found that it contains a new DNA binding domain and binds to specific DNA sequences as a monomer. Skn-1 recognizes a DNA binding site similar to a bZIP half site and also recognizes an AT-rich sequence adjacent to this half site. The AT-rich sequence is recognized by a region of the protein that resembles the amino-terminal arm of a homeodomain protein.

### Poles and position

In *Drosophila*, the cytoskeleton of the oocyte is polarized and is involved in the localization of maternal determinants that establish the anterior-posterior (AP) axis. González-Reyes and



St Johnston (p. 639) examined how AP asymmetry is generated during the early stages of oogenesis. Early movement of the oocyte to the posterior of the egg chamber determines AP asymmetry in the oocyte and in the somatic follicle cells. The establishment of the AP axis requires signaling from the oocyte to the follicle cells and back.

### Baboons and AIDS

Chimpanzees and pig-tailed macaques are the main nonhuman primates currently used to study human immunodeficiency virus (HIV) infection, but infection in these species does not progress into a disease like acquired immunodeficiency syndrome (AIDS). Both of these animal models have other drawbacks, such as cost and a lack of persistent infection. Barnett *et al.* (p. 642) show that persistent infection of baboons with HIV-2 can be achieved and that some animals exhibit AIDS-like symptoms, including lymph node pathologies and declining $CD4^+$ cell counts.

### Change of preference

The sequence-specific interaction of proteins and peptides with nucleic acids relies largely upon precise recognition of the donors and acceptors arrayed on the bases. Geierstanger *et al.* (p. 646) present the culmination of studies designed to reverse the affinity of distamycin, a natural product, for regions of DNA that contain tracts of AT base pairs. They arranged the same heterocycles present in distamycin to create a ligand that binds to GC sequences. Structural analysis indicates that the specificity within the 2:1 ligand:DNA complex is governed by the hydrogen bonding between pyrrole nitrogens and guanine amino groups.

### Nuclei option

Transgenic embryos have been used to great advantage in studying development of mouse and *Drosophila*. However, in a great variety of otherwise informative systems, including the frog *Xenopus*, the standard approach to transgenesis is not available. Kroll and Gerhart (p. 650) transplanted nuclei from a cell line into *Xenopus* eggs. The cell line can be stably transfected with the plasmid of choice before the transplantation procedure, such that the resulting embryos will carry the transgene without having to go through generations of propagation.

### Found in translation

The rate of protein synthesis is increased in cells treated with insulin or growth factors. Lin *et al.* (p. 653; see news story by O'Brien, p. 542) describe a biochemical signaling mechanism that appears to account for this effect. PHAS-I is an inhibitor of initiation factor 4E (eIF-4E). Insulin and other growth factors stimulate mitogen-activated protein (MAP) kinase. MAP kinase phosphorylates PHAS-I and causes its dissociation from eIF-4E, thus enhancing the activity of eIF-4E in the initiation of translation.

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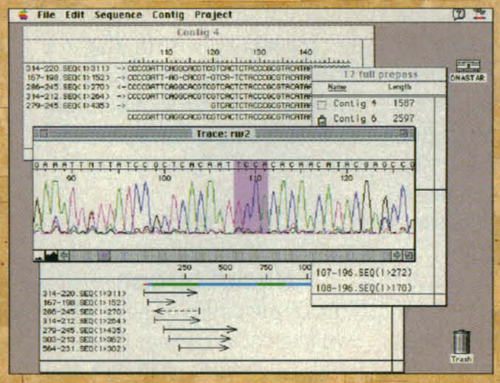


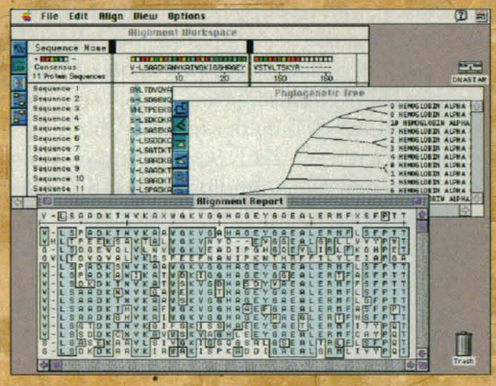


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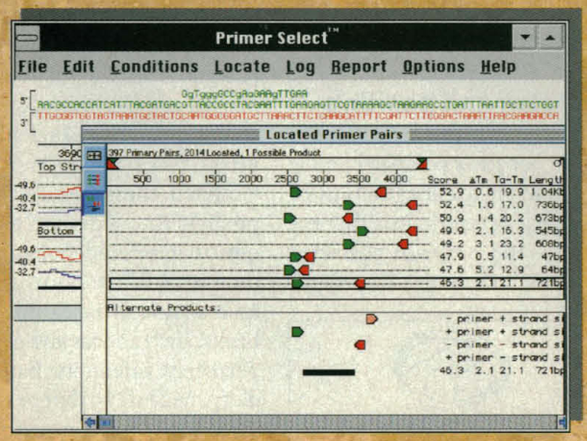


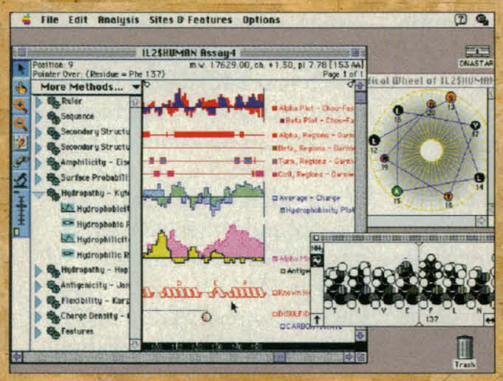


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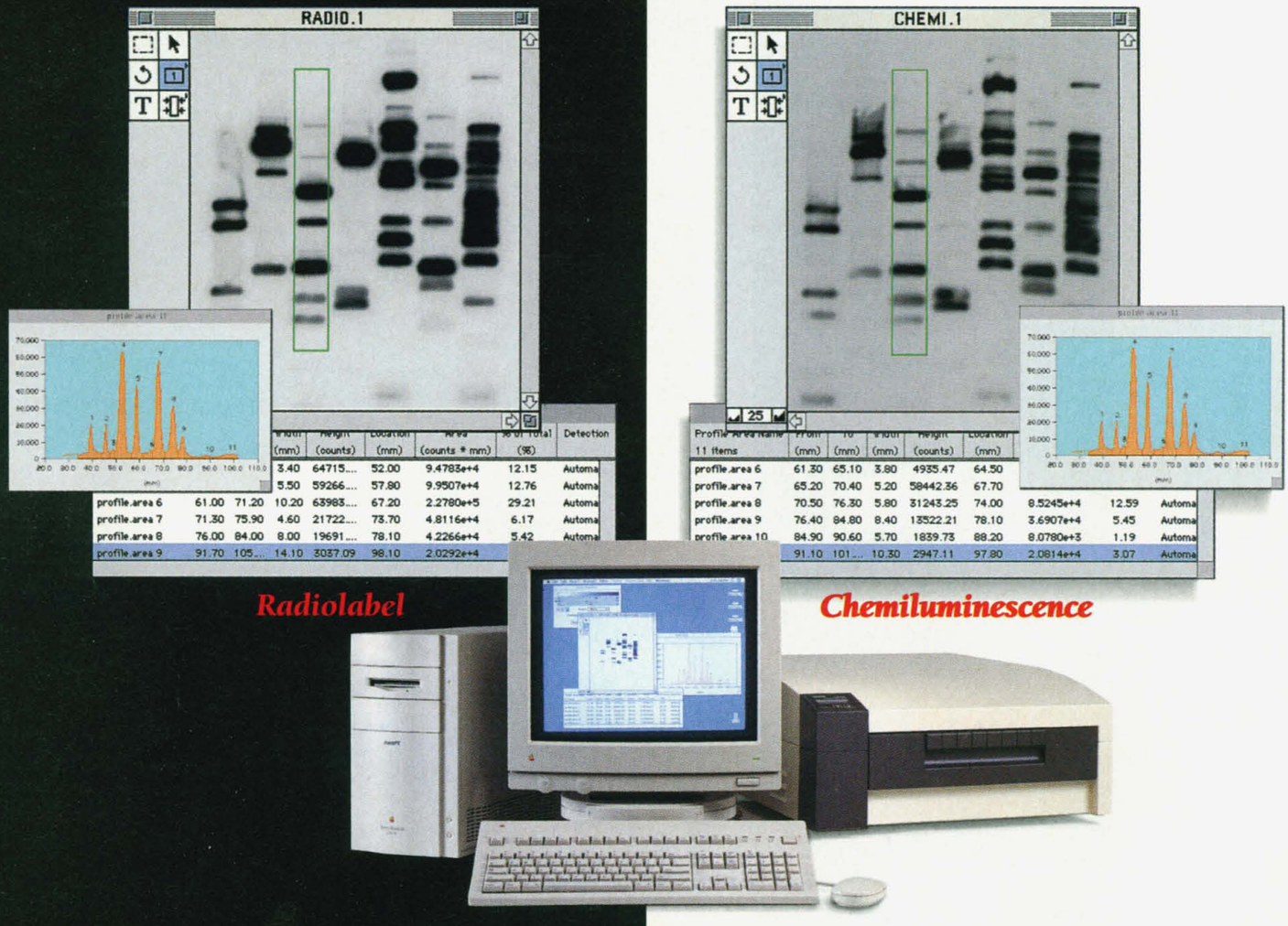


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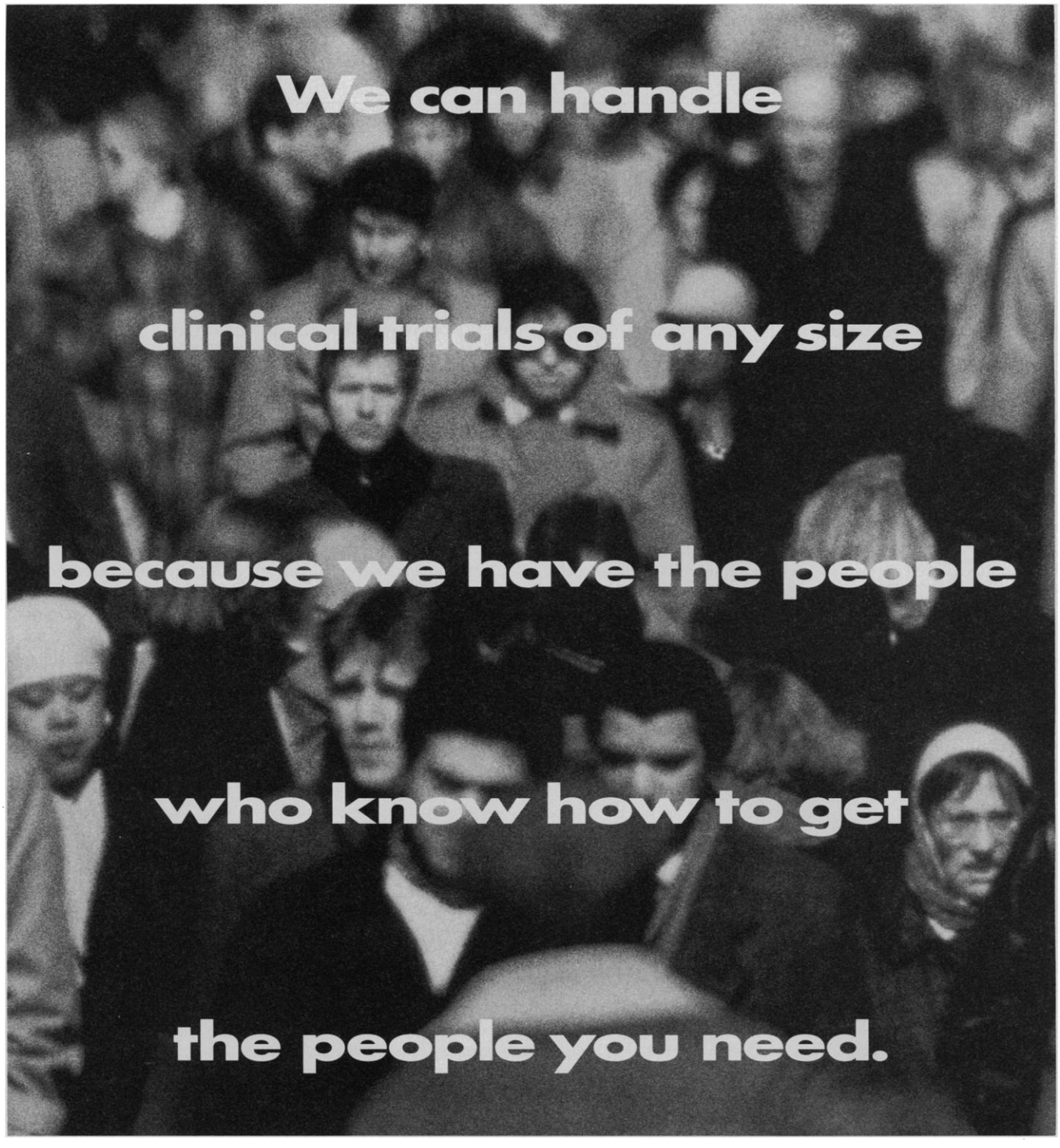


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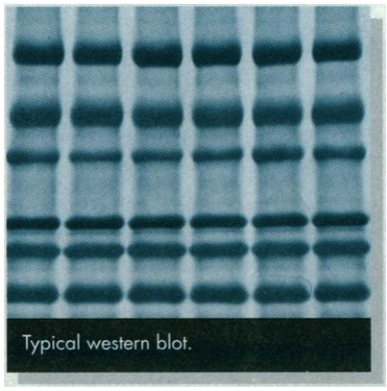

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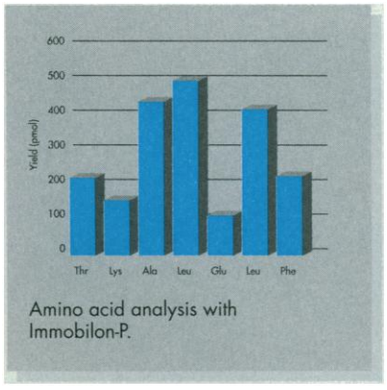


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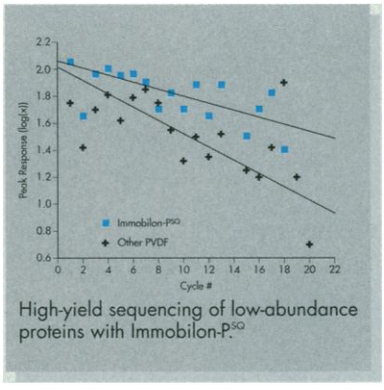


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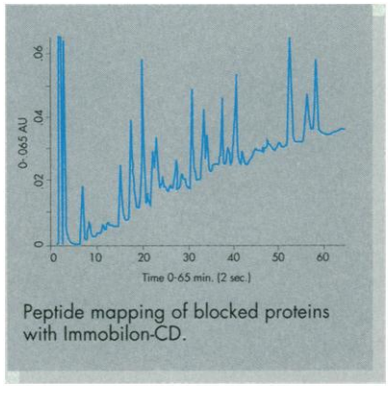


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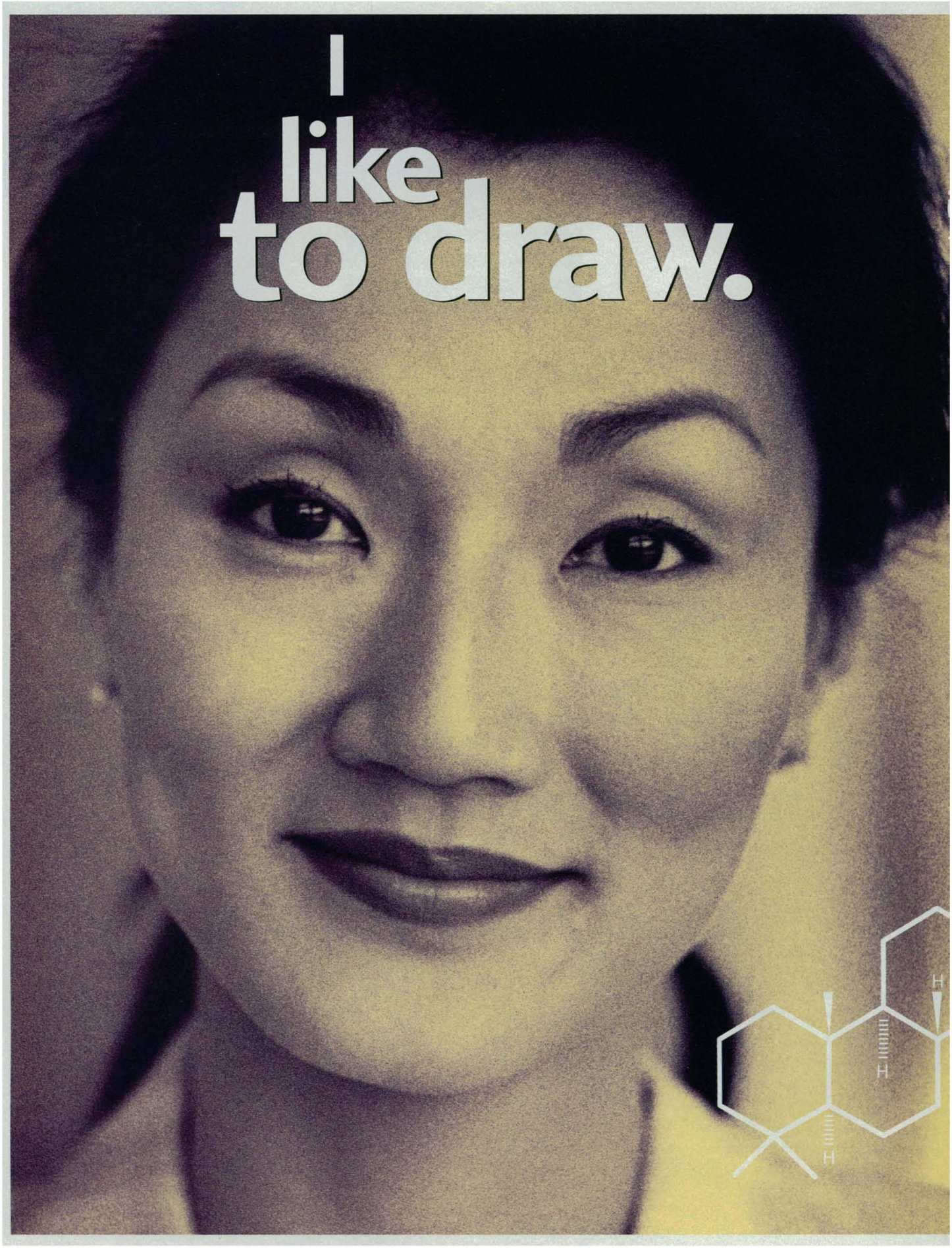
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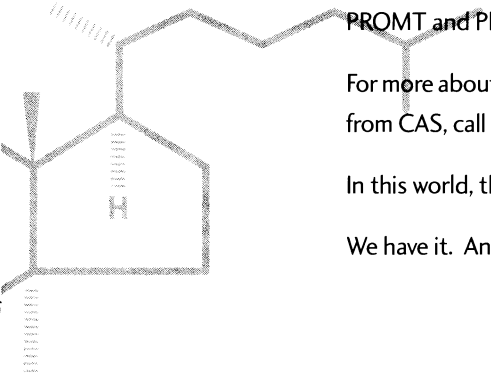

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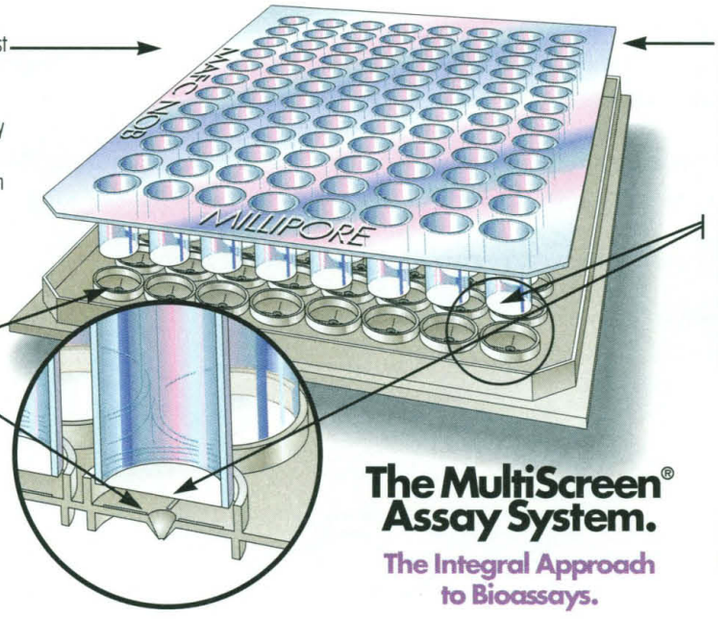


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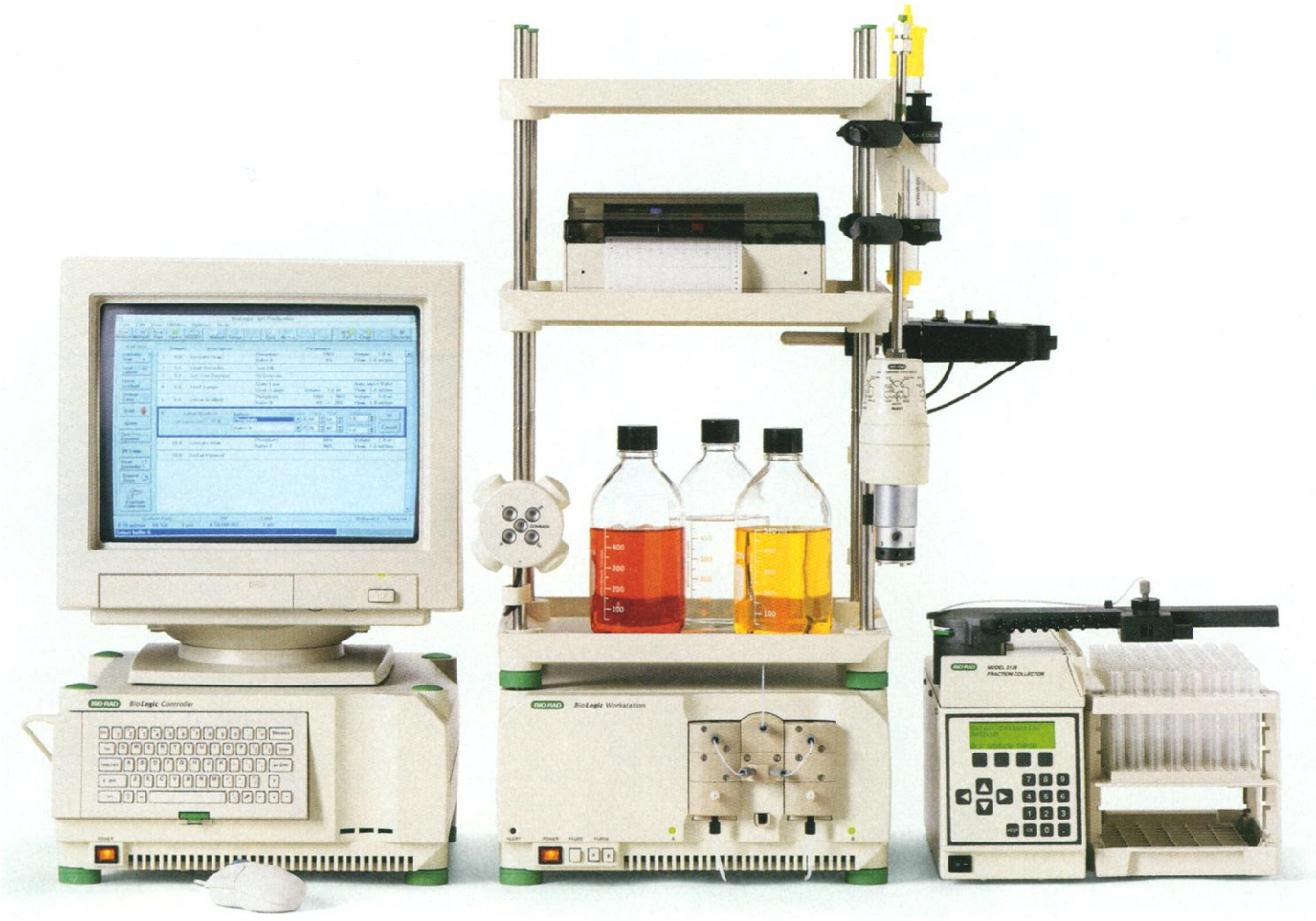

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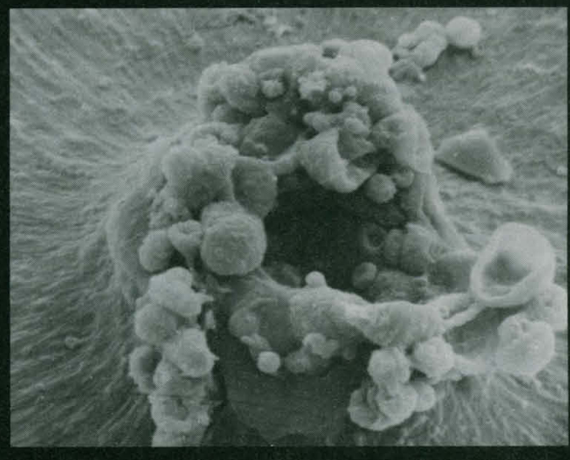

*Scanning electron micrographs of primary rat mammary epithelial cells at 24 hours (inset) and 36 hours (background) on MATRIGEL® Basement Membrane Matrix. Photo courtesy of Dr. Margaret Neville.*

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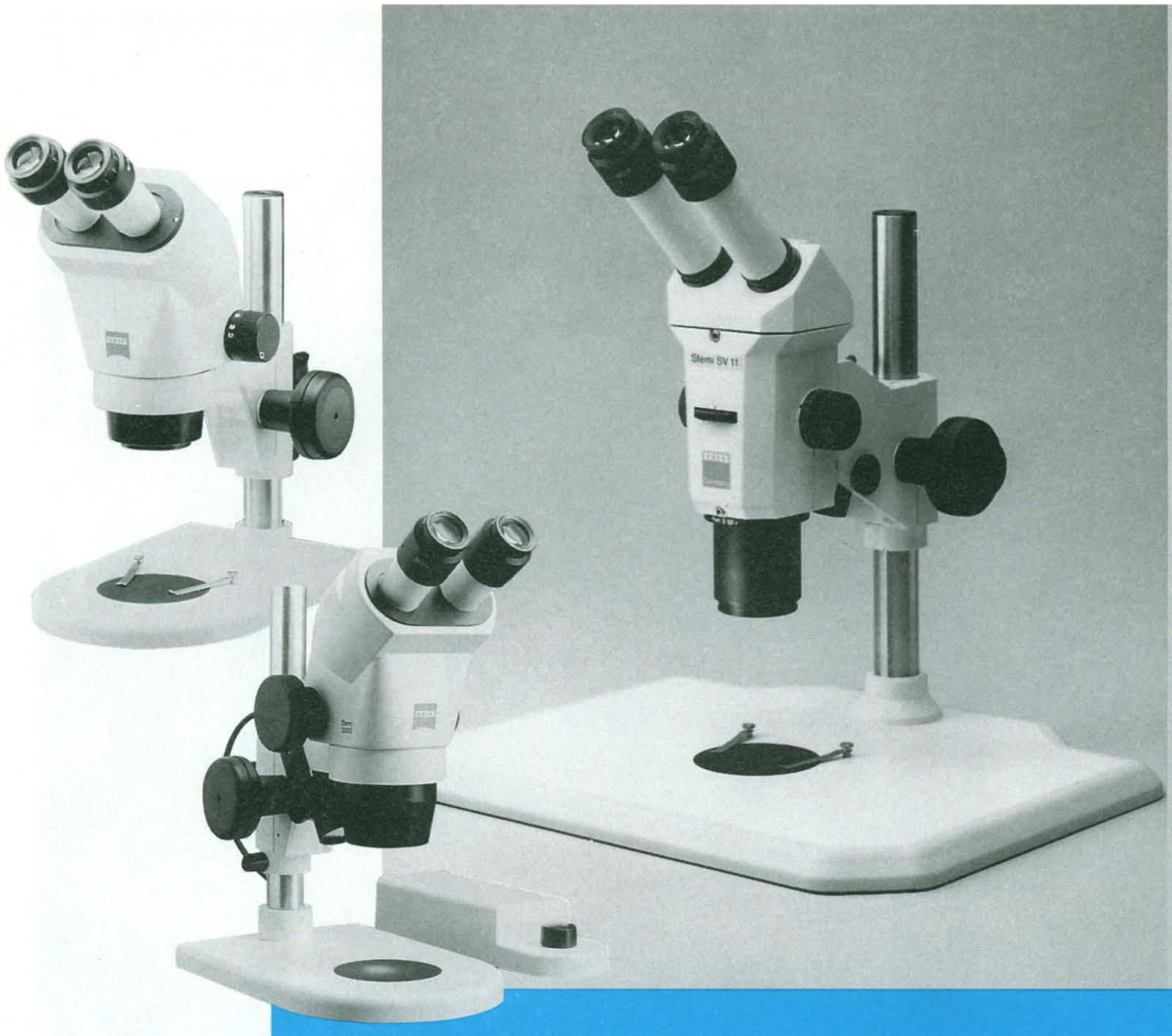


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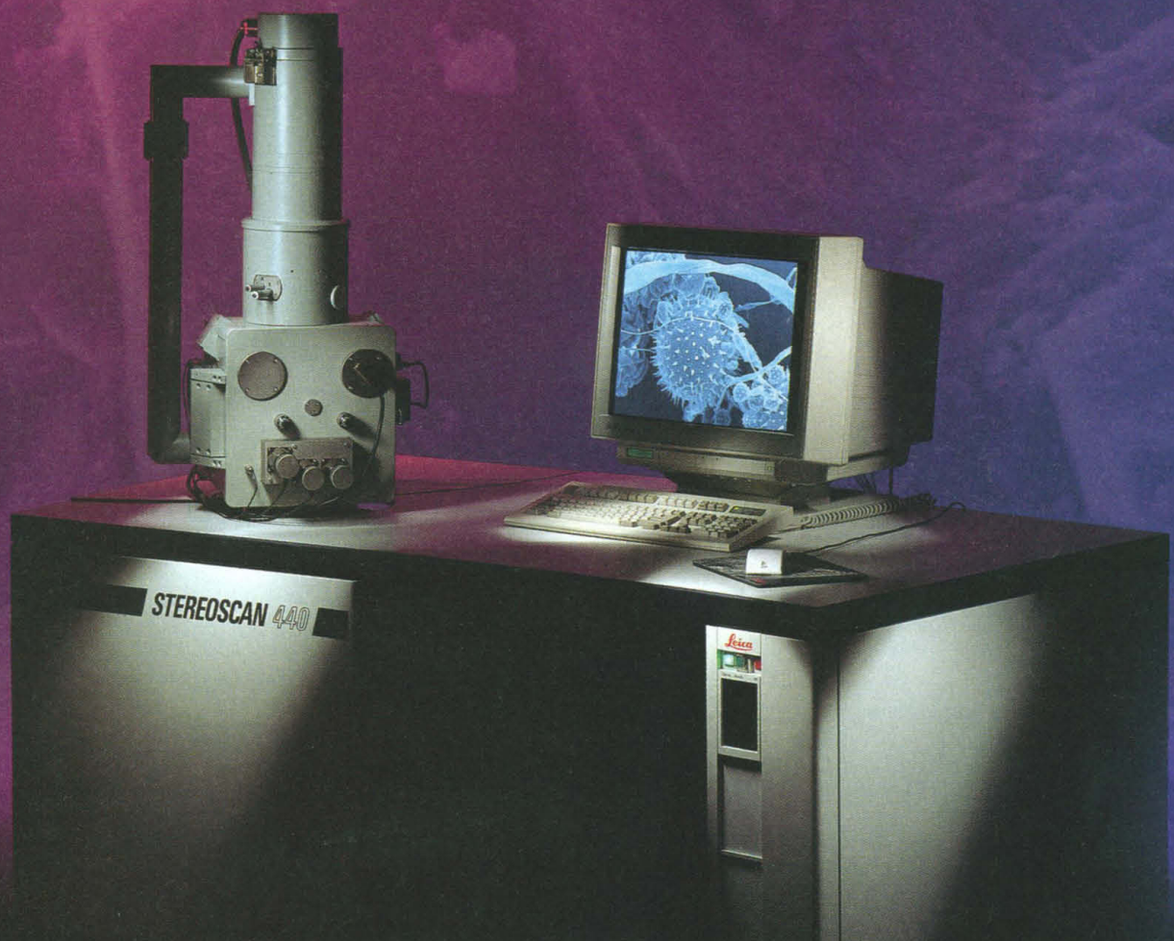


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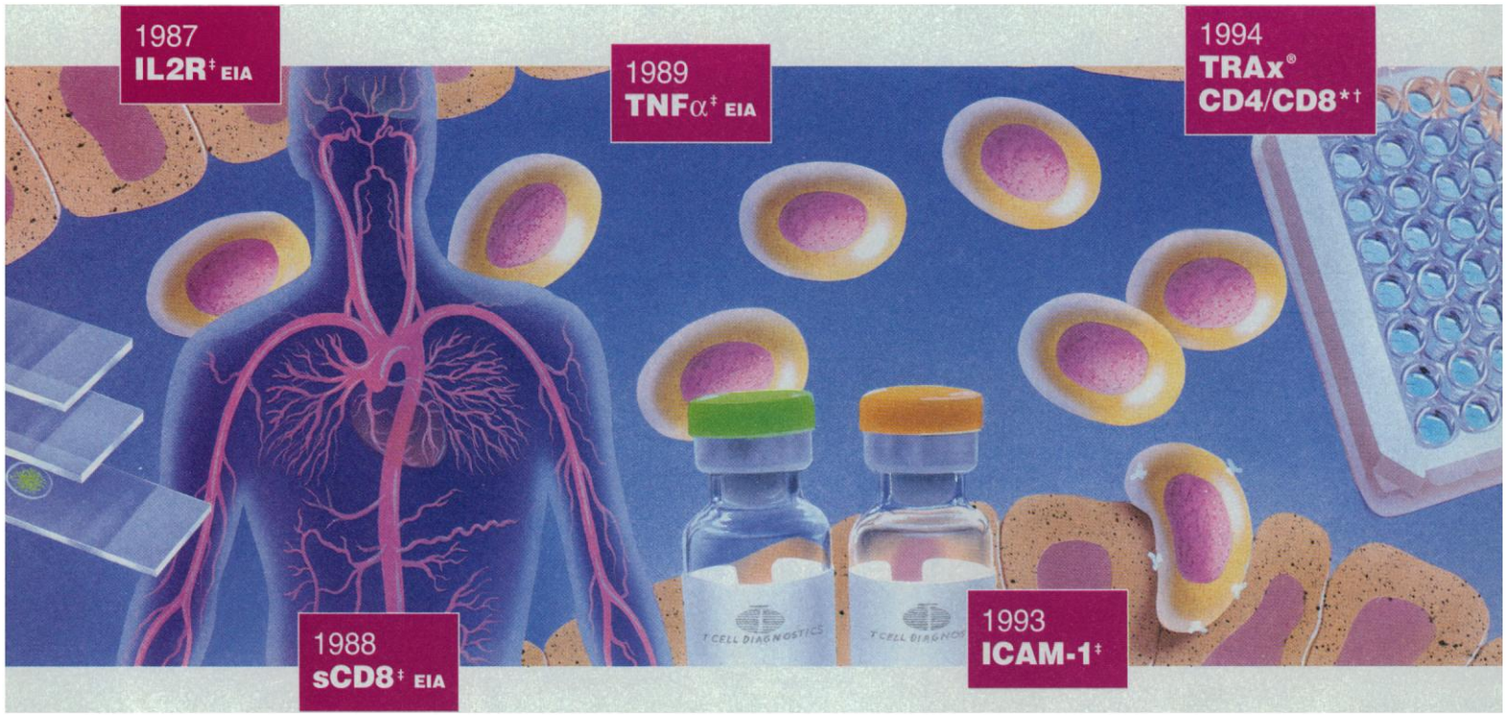


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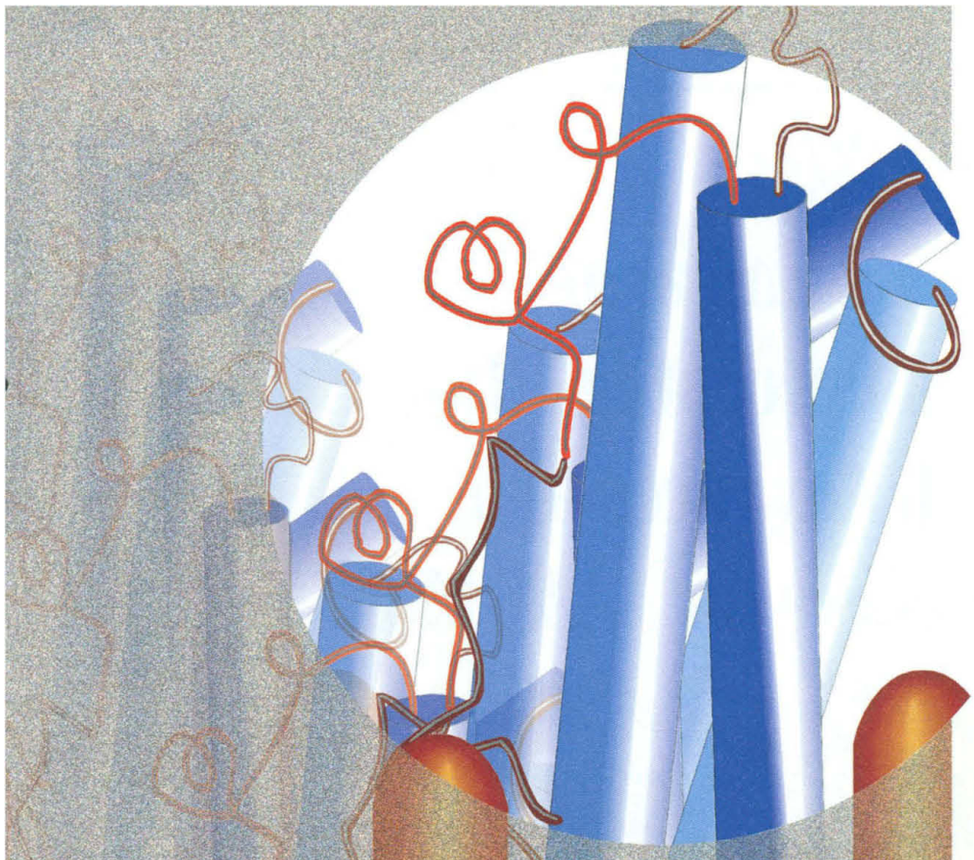

# Biomolecular Interaction Analysis - the shortest route between structure and function

*Comparison of a structural and functional binding domain in human growth hormone using real-time BIA*

*B. C. Cunningham and J. A. Wells*
*(J. Mol. Biol. (1993) 234, 554-563)*

From a structural point of view, the complex between human growth hormone (hGH) and the extracellular domain of its receptor (hGHbp) is one of the best characterized hormone-receptor complexes. One molecule of hGH binds sequentially to two molecules of hGHbp, involving separate sites on the hormone molecule and resulting in dimerization of the receptor.

The work of Brian C Cunningham and James A Wells of Genentech Inc, USA, used Biomolecular Interaction Analysis (BIA) to measure the progress of the macromolecular interactions in real-time, allowing the evaluation of the kinetics as well as the affinity of the interactions. By this method it was possible to determine the effect of replacing each of the 30 contact residues in the hGH site 1 structural binding domain with alanine.

The results indicated that only one quarter of the residues account for the major part of the binding energy. Thus the functional binding domain is considerably smaller than the structural binding domain. The results are potentially valuable in the design of hormone analogues for therapeutic purposes, identifying critical residues for the binding interaction and implying that it might be possible to design smaller hormone mimics.

Establishment of a clearly defined experimental situation for the real time BIA studies was aided by the specific immobilization chemistry on the sensor chip. By immobilizing the receptor through a single cysteine residue introduced at a chosen position, the properties of the surface-bound interaction could be closely controlled. This work clearly demonstrates the value of real-time BIA in analysing functional aspects of macromolecular interaction.

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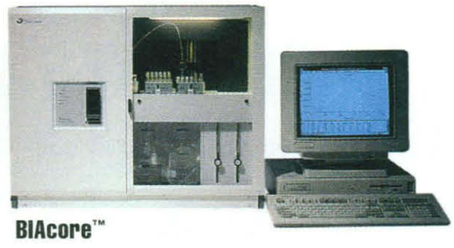

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## If you're working with DNA or protein, you're ready to work with carbohydrates

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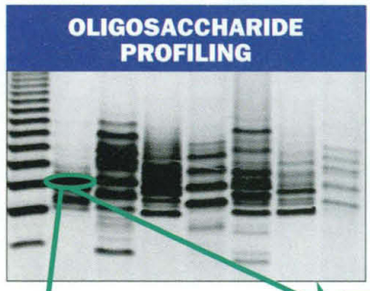
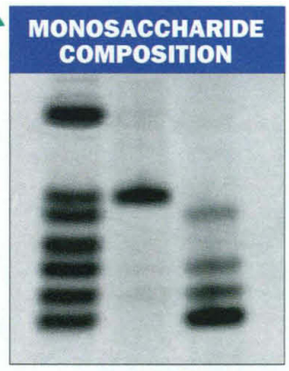
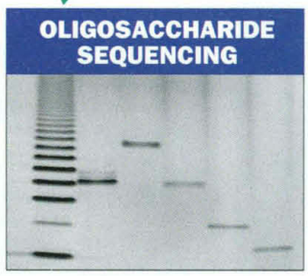
Now, in less than one day, you can perform profiling, composition, or sequencing experiments such as the ones shown here, using FACE chemistry kits.




**FACE gel profile of N-linked oligosaccharides released from a number of different glycoproteins**




**FACE gel showing the monosaccharide compositional analysis of a tri-sialylated, triantennary oligosaccharide**

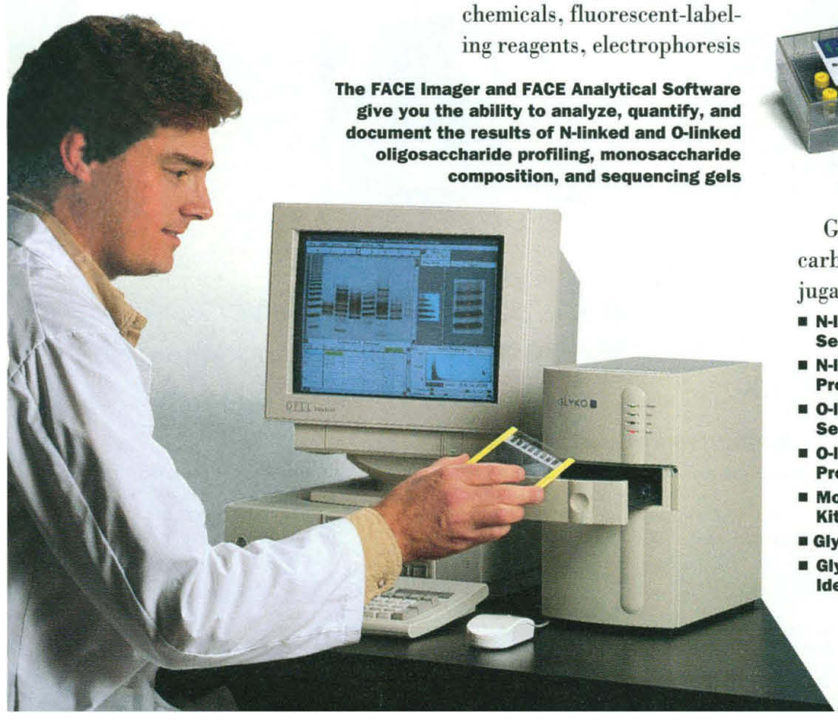



**FACE gel illustrating the enzyme-based sequencing of a tri-sialylated, triantennary oligosaccharide**

## Color-coded FACE kits make carbohydrate analysis easy and reliable

FACE kits are color-coded and are designed to provide a complete approach to carbohydrate analysis...starting with the enzymatic or chemical release from the glycoconjugate to the separation, isolation, or sequencing of oligosaccharides.

Everything you need is included: enzymes or release chemicals, fluorescent-labeling reagents, electrophoresis standards, controls, running buffers, precast polyacrylamide gels, and complete protocols.



**The FACE Imager and FACE Analytical Software give you the ability to analyze, quantify, and document the results of N-linked and O-linked oligosaccharide profiling, monosaccharide composition, and sequencing gels**

Glyko FACE kits for carbohydrate or glycoconjugate analysis include:

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## Sequence your oligosaccharides with Glyko recombinant glycosidases

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- **NANase I:** *releases α2-3 N-acetylneuraminic acid*
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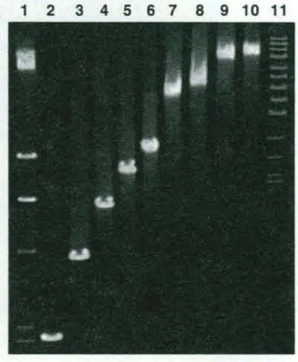
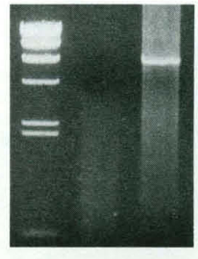



Lane 1 λDNA/*Hin*d III marker
Lane 2 2.0 kb
Lane 3 4.0 kb
Lane 4 6.0 kb
Lane 5 8.0 kb
Lane 6 10.0 kb
Lane 7 18.0 kb
Lane 8 20.0 kb
Lane 9 28.1 kb
Lane10 30.0 kb
Lane11 High MW marker

**#2 Genomic DNA fragment of 6.8 kb was specifically and efficiently amplified by genome walking on the *E. coli* chromosome with this LA PCR Kit employing Single Specific Primer PCR and Nested PCR.**




Lane 1 λDNA/*Hin*d III marker
Lane 2 Conventional PCR kit
Lane 3 LA PCR Kit


*1 Shyamala, V. and Ames, G.F.-L.: Genome walking by single-specific-primer polymerase chain reaction: SSP-PCR. *Gene* **84** (1989) 1-8

*2 Isegawa, Y. *et al.*: Selective amplification of cDNA sequence from total RNA by cassette-ligation mediated polymerase chain reaction (PCR): Application to sequencing 6.5 kb genome segment of hantavirus strain B-1. *Molecular and Cellular Probes* **6** (1992) 467-475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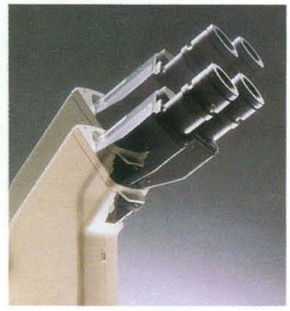

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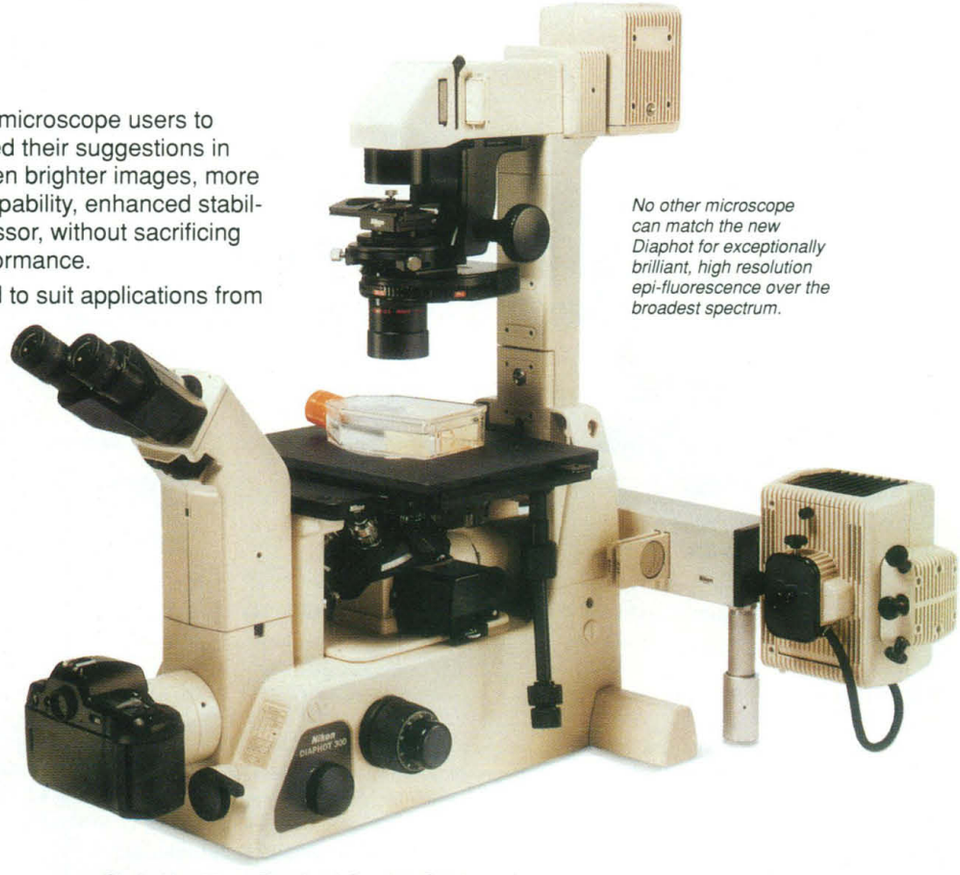


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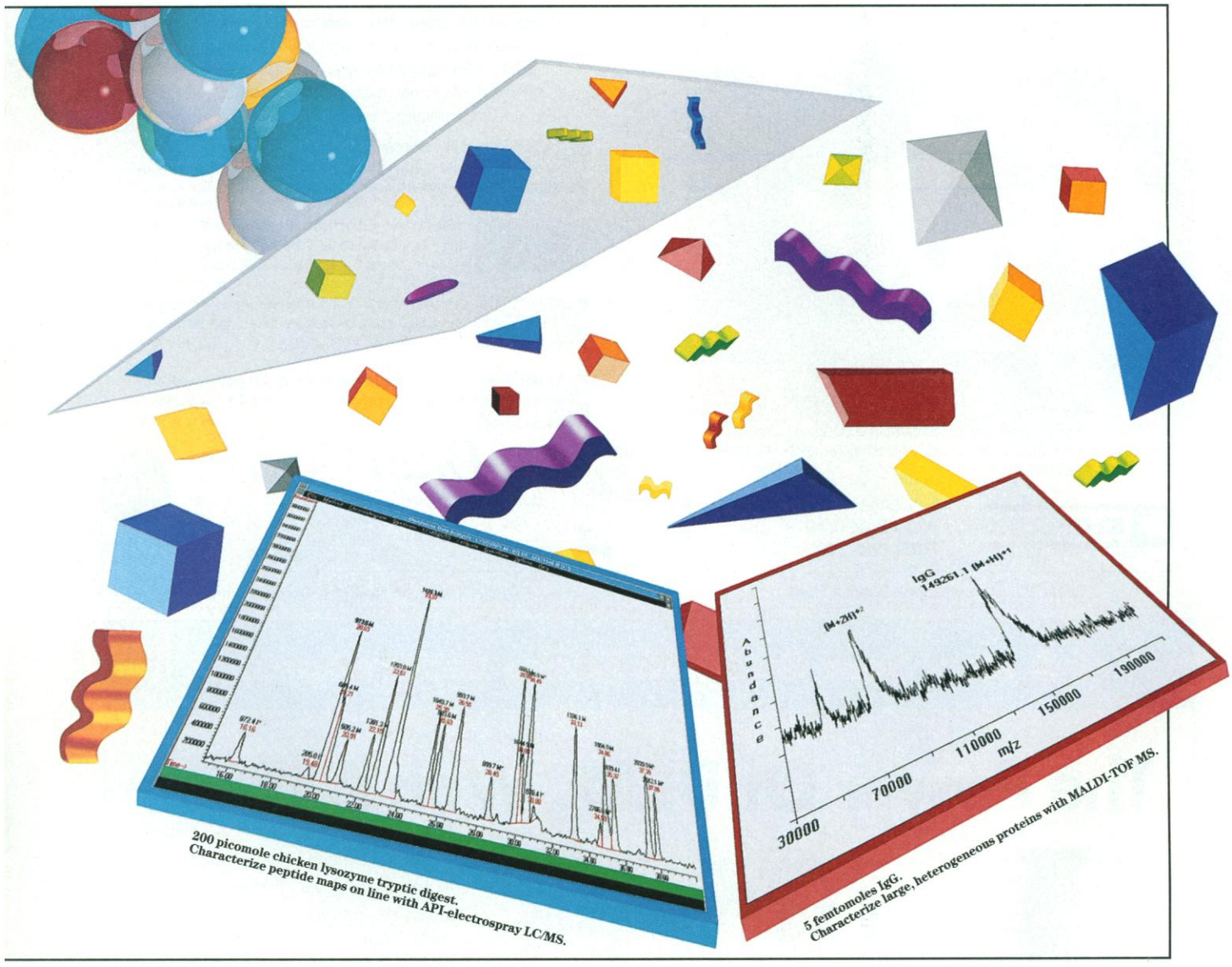


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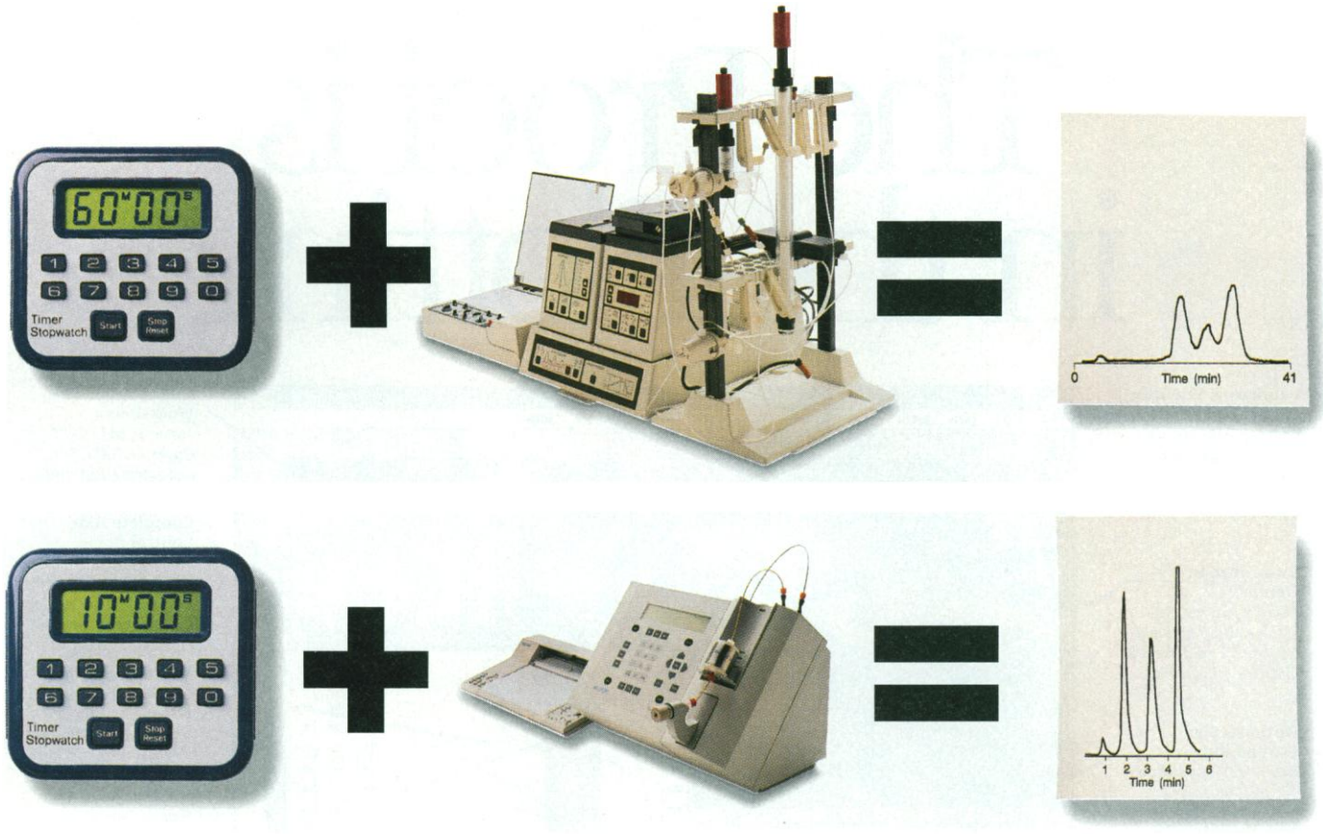


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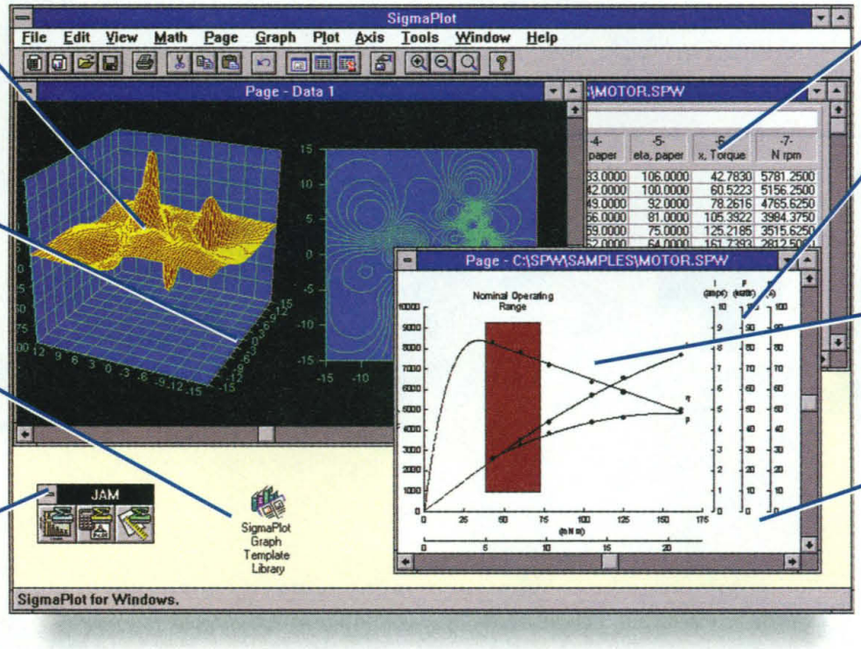


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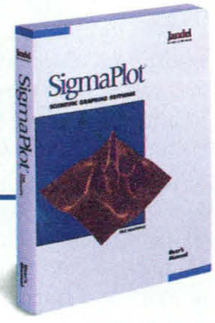


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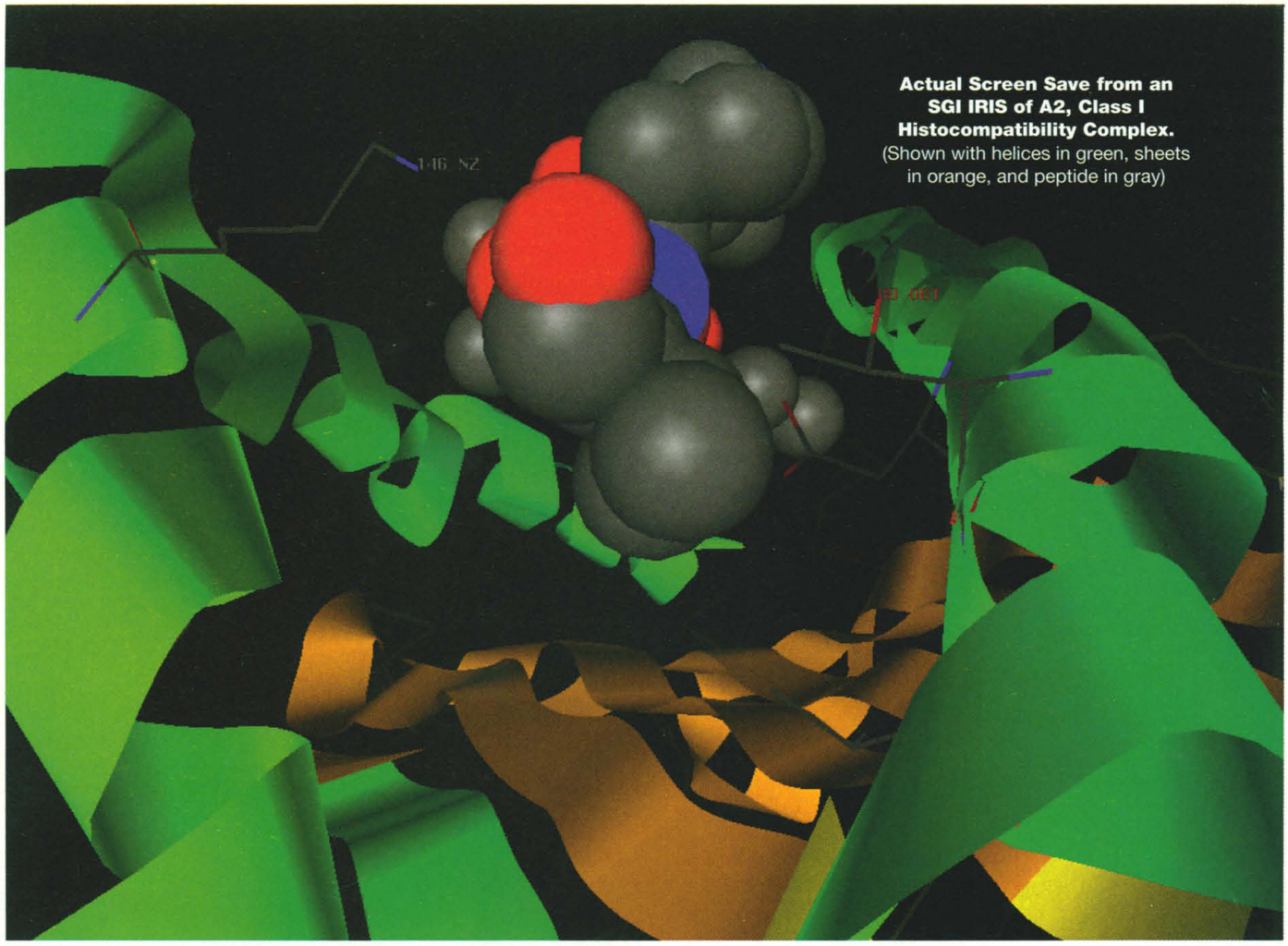

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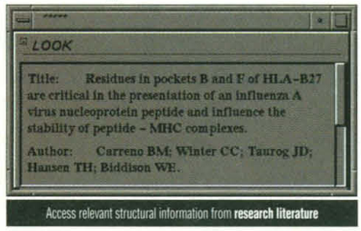


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