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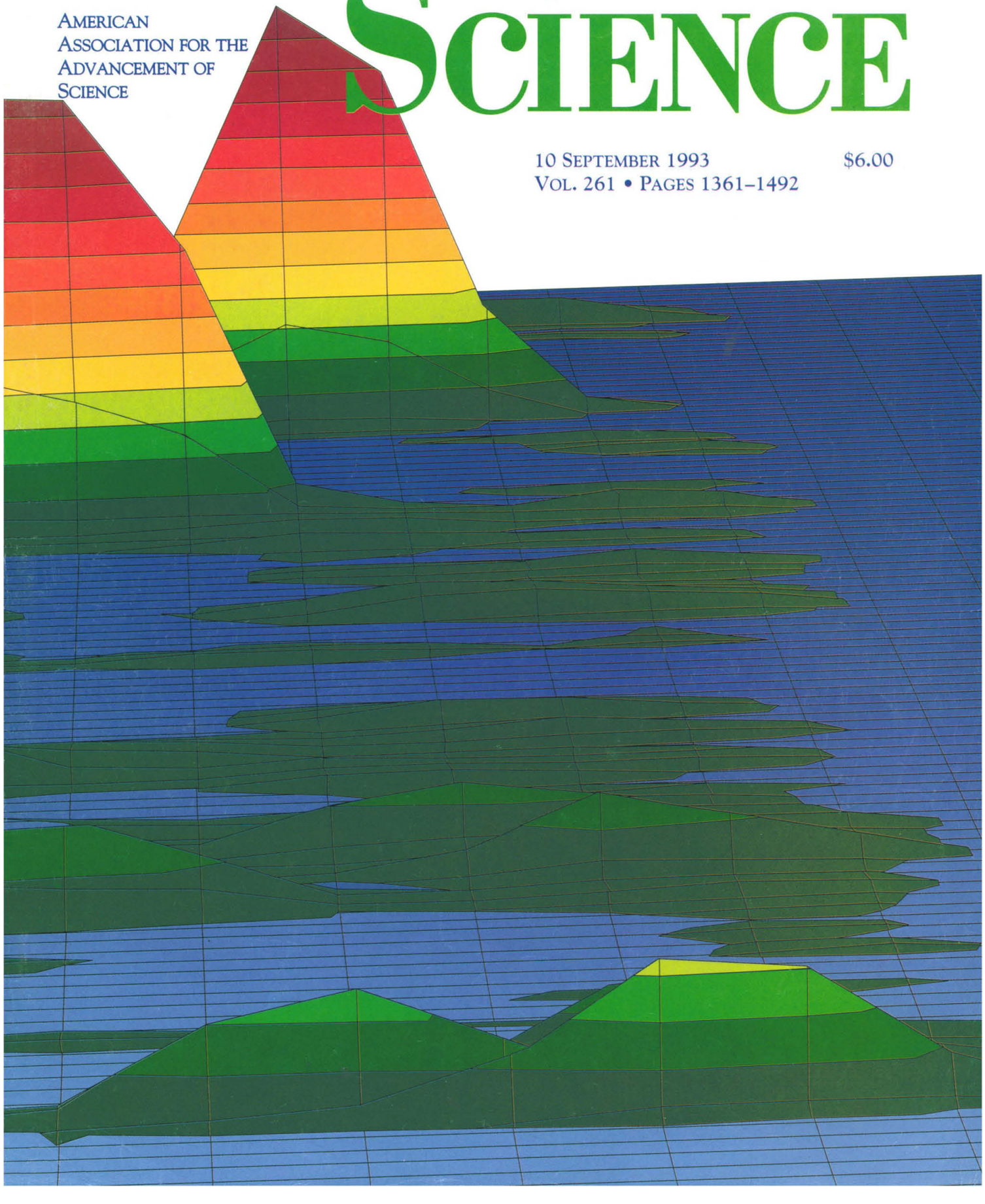

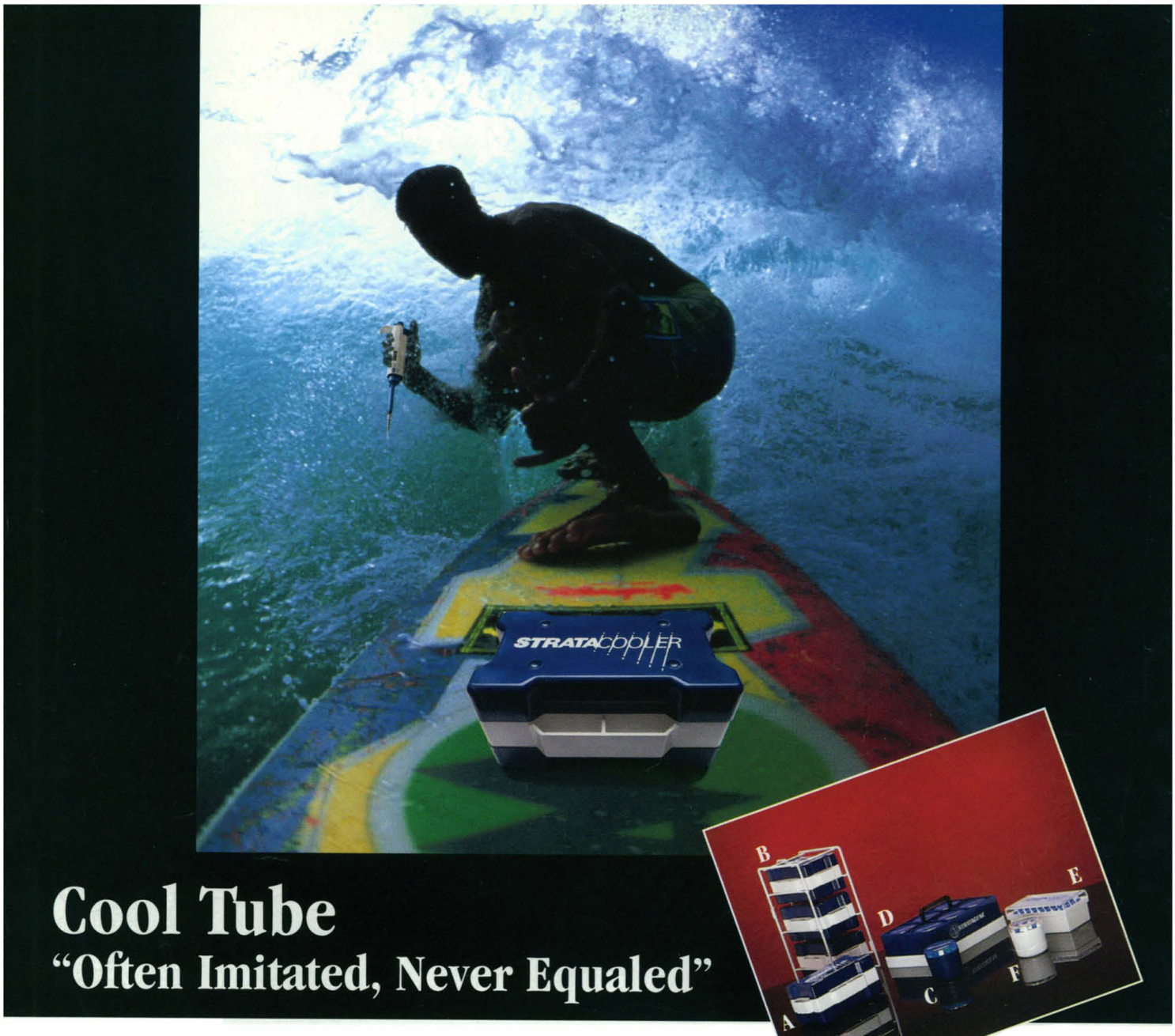

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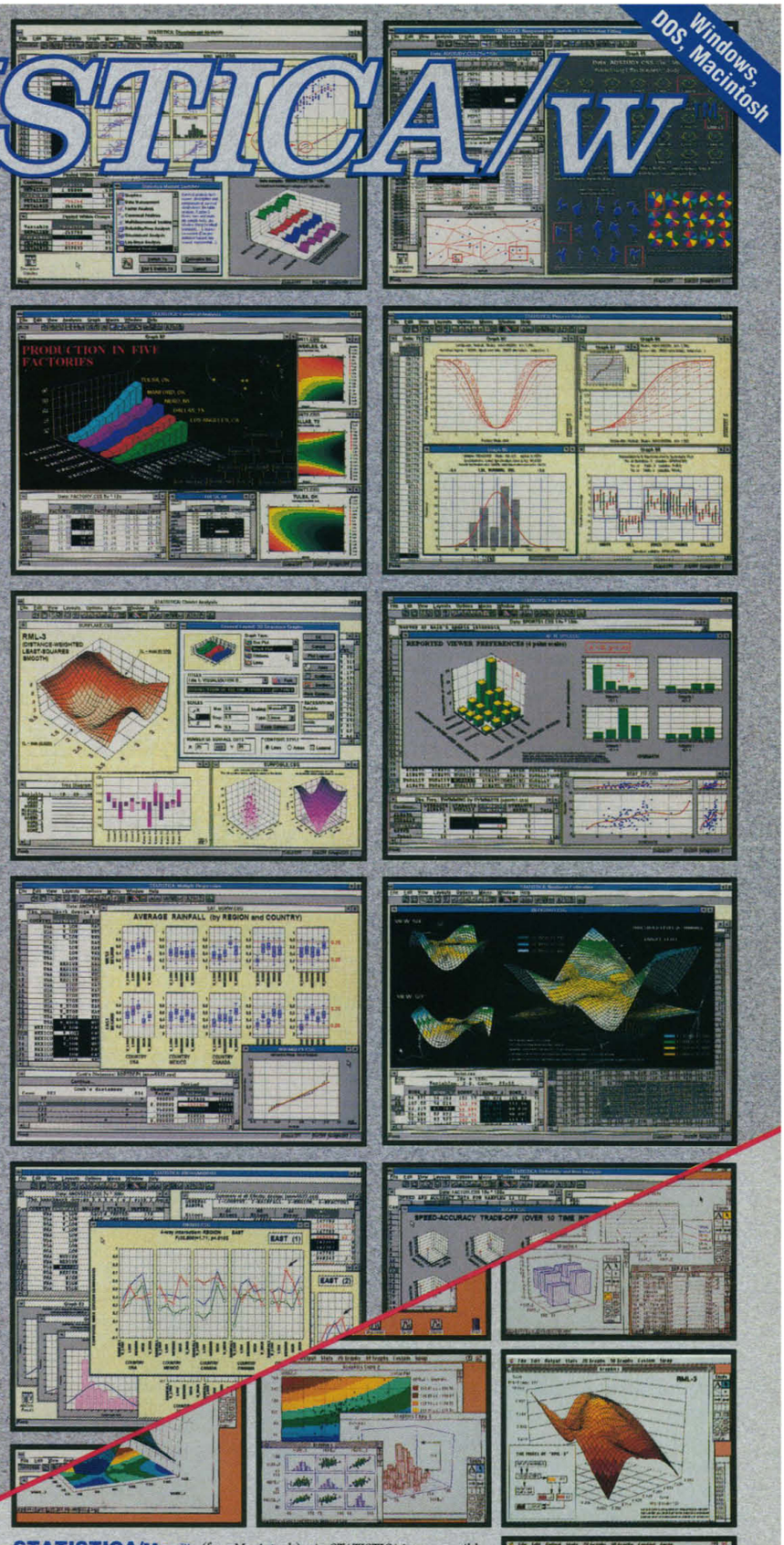

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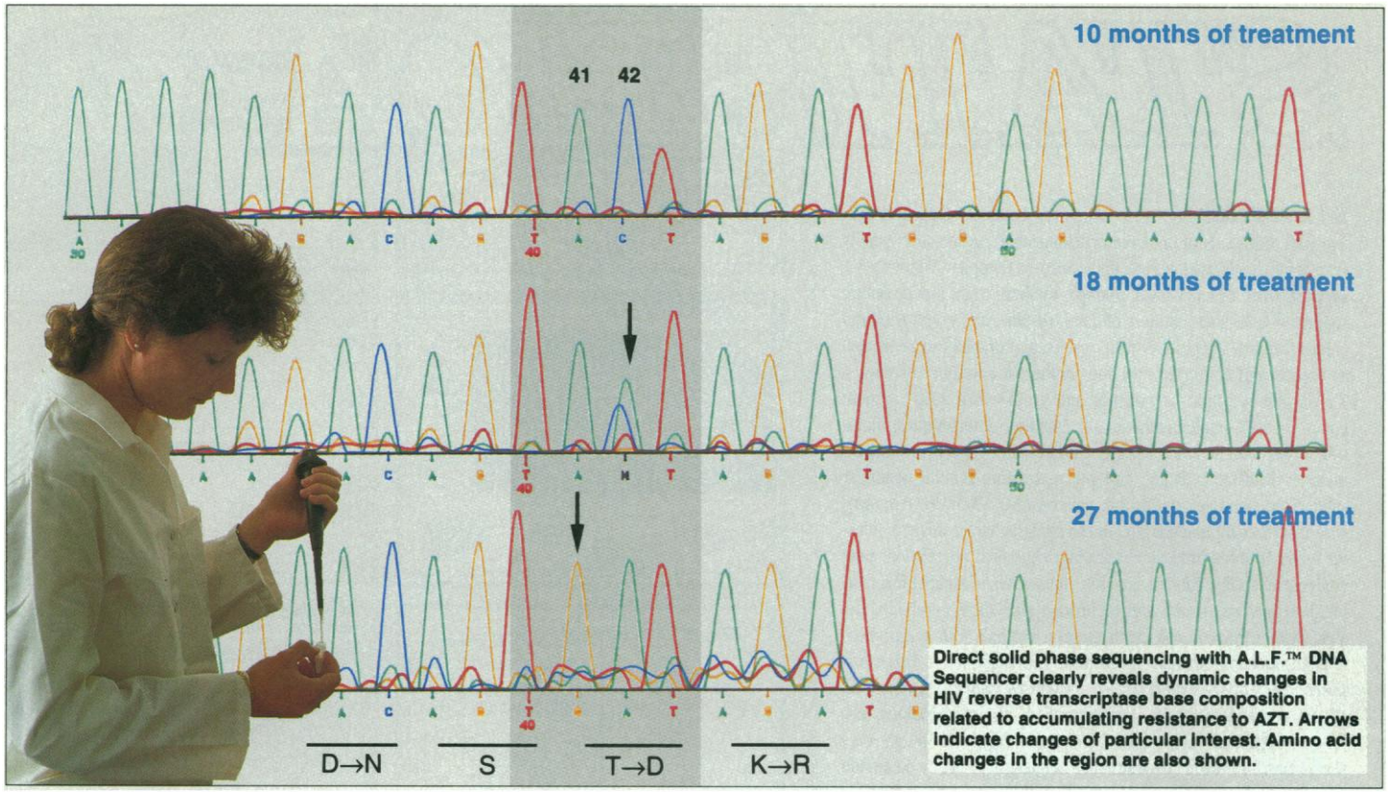


Direct solid phase sequencing with A.L.F.™ DNA Sequencer clearly reveals dynamic changes in HIV reverse transcriptase base composition related to accumulating resistance to AZT. Arrows indicate changes of particular interest. Amino acid changes in the region are also shown.

A.L.F.™ DNA Sequencer helps AZT fight HIV

Accurate detection of heterozygote point mutations has enormous potential as a clinical research tool. Nothing illustrates this better than the recent spectacular analysis of emerging AZT resistant HIV species by direct, solid phase genomic sequencing with A.L.F.™ DNA Sequencer.

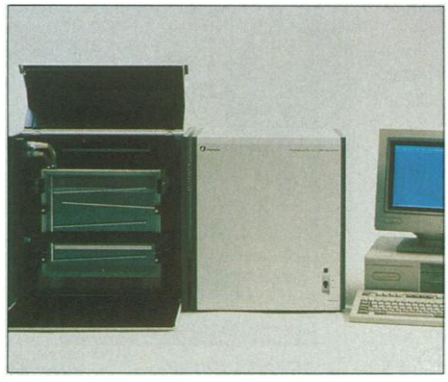
The non-edited data output above shows DNA sequences of HIV RT from a patient undergoing AZT treatment[1]. This clean sequence with little background signal emphasizes the suitability of A.L.F. for direct genomic sequencing of clinical samples. Detailed analysis revealed dynamic changes in base composition.

Take a close look at the changes A.L.F. detected at position 42. The C residue after 10 months treatment became a 50% A/C mixture at 18 months and a clear A nucleotide at 27 months. With a secondary shift from A to G at position 41, Thr69 changed to Asp, a substitution not previously reported.

Only the Automated Laser Fluorescent detection system of A.L.F. combines all the advantages for detecting point mutations like these.

Fixed laser detection of sample bases is essential to reduce background noise. With its unique fixed laser (A.L.F has no moving parts apart from the door), background noise is lower than other sequencers. Hence its base calling is more accurate.

And because A.L.F. uses just one single fluorescent label, you don't have to worry about spectral overlaps and mobility shifts, which again makes base calling more accurate.



A.L.F. DNA Sequencer accurately detects heterozygote point mutations. DNA sequencing with A.L.F. has many applications in clinical research.

Furthermore, the well-proven Sanger technique, already cited more than 20,000 times, leaves nothing to chance with the reaction chemistry.

A.L.F. thus provides the accuracy needed to yield the "consensus" sequence of viral genomes in samples from HIV-1 infected patients treated with AZT.

So with A.L.F. generating precision data like this, clinical researchers can rapidly determine the molecular basis for drug resistance and more effectively plan treatment with alternative drugs or combinations of drugs. And, of course, direct DNA sequencing with A.L.F. has plenty of other clinical applications in areas such as infectious diseases, cancer, genetic disorders and forensics.

Ask for more details and a reprint of the reference.

1. Dynamic changes in HIV-1 quasispecies from azidothymidine (AZT) treated patients. *FASEB Journal 6 (1992)*,Wahlberg, J., Albert, J., Lundeberg, J., Cox, S., Wahren, B., Uhlén, M.

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(9203)

PROTEINS

How innovative technologies solve today's problems.

Today's protein research environment is more exciting and demanding than ever before. With each breakthrough, researchers discover new challenges as they strive to do more in less time with smaller amounts of material. In many cases, they are solving these problems with the application of alternate technologies.

PROTEIN QUATERNARY STRUCTURE: WHERE DO TRADITIONAL TECHNIQUES FALL SHORT?

Quantification of stoichiometry and binding affinities is critical, both in quality control of recombinant proteins and in anti-viral drug development. Yet direct measurement of these thermodynamic properties has been hampered by empirical methods that rely on molecular weight standards and unjustified assumptions or methods that interfere with equilibrium between associated and non-associated protein moieties. To avoid such problems, Beckman Instruments now offers a modern analytical ultracentrifuge described by Dr. Preston Hensley of SmithKline Beecham:

"The analytical ultracentrifuge is the ideal analytical tool. It allows us to define assembly processes in viruses and has been extremely helpful to us in characterizing proteins that may be incorrectly folded as the result of particular expression protocols. The XL-A Analytical Ultracentrifuge has made a key contribution to our drug discovery efforts."

MAXIMIZING SEQUENCER PRODUCTIVITY: CAN NEW TECHNOLOGY CROSS-CHECK SAMPLE PURITY *BEFORE* SEQUENCING?

Separation scientists continually find that the isolation and purification of a sample prior to sequence are more difficult and time-consuming than the sequencing itself. Reverse-phase HPLC is well-established but does not provide an adequate verification of purity.

Beckman Instruments has successfully demonstrated how a combination of technologies — HPLC and capillary electrophoresis (CE) — can efficiently verify purity and solve the problem of wasted sequencer time. CE performs purity analysis in a fraction of the time spent with more traditional techniques.

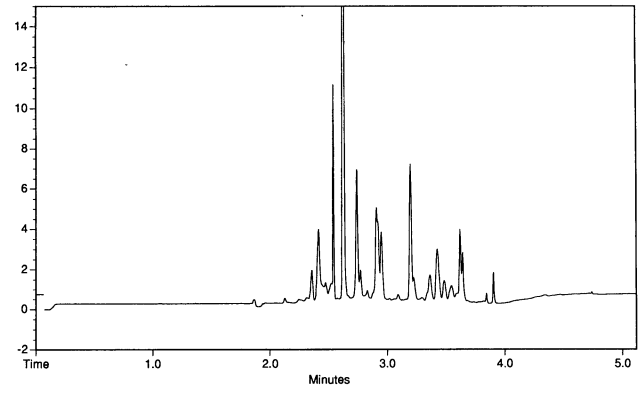
The 1990-91 Annual Report of the University of Cambridge Centre for Molecular Recognition reports:

"The Beckman P/ACE™ capillary electrophoresis apparatus has exceeded our expectations of usefulness and this instrument heralds a very exciting future in the study of biological molecules. Its speed and sensitivity have made it the preferred choice to HPLC in the analysis of protein and peptide purity in many cases; preparative work continues to be done by HPLC."

Beckman has integrated HPLC and CE with its Gold software, producing the only LCCE system available today. With the Porton LF 3000 Protein Sequencer, Beckman provides a complete protein workstation for the determination of primary structures.

COMPOUND DETECTION: IS THERE A WAY TO GET HIGH RESOLUTION *AND* HIGH SENSITIVITY?

With its speed and resolution, CE is increasingly being used for the study of microsamples and peptide fragments. And now, to counter its inherent sensitivity limitation, Beckman offers a laser-induced fluorescence (LIF) detection option that expands detection limits to the femtomolar range.



Tryptic digest of β-lactoglobulin analyzed with CE. (700 attomoles injected.)

For more information about applications of the techniques discussed in this article, the Beckman Plus, or for information and dates on Beckman's worldwide Protein Discovery Tour, write to Beckman Instruments, Inc., Bioanalytical Systems Group, 2500 Harbor Boulevard, Fullerton, California 92634-3100. Or call, toll-free in the U.S.A. 1-800-742-2345.

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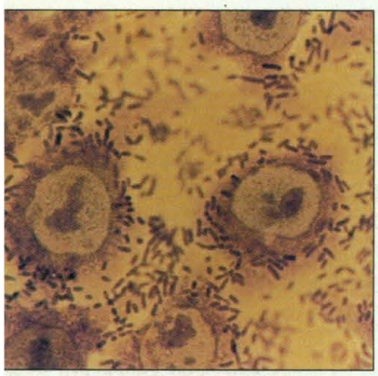


1390 & 1454
New TB model

NEWS & COMMENT

RESEARCH NEWS

PERSPECTIVES

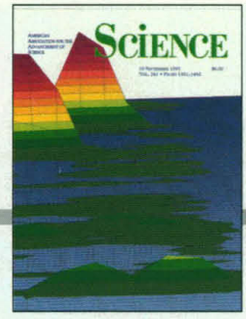
ARTICLE

RESEARCH ARTICLES

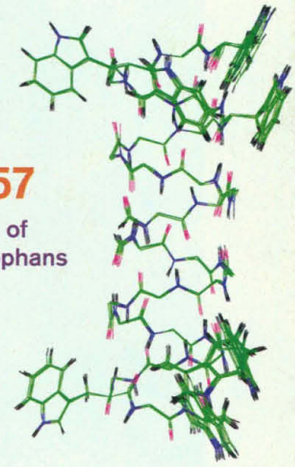
DEPARTMENTS

COVER

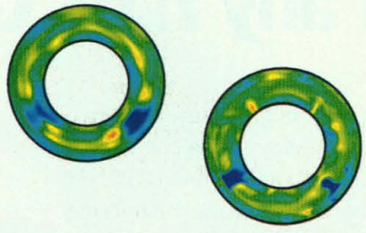
Catalytic RNAs (ribozymes) emerging from a pool of random sequence RNA (blue) in response to in vitro selective pressure for catalytic activity. After an initial increase in abundance to detectable levels (green), with mutation and continued selection some improved catalysts come to dominate the population (red). Such in vitro manipulation can result in a population of new ribozymes with desired specificity. See page 1411 and the Perspective on page 1402 . [Image: David Bartel, source; Tracy Keaton, additional illustration]



REPORTS



1457
A tale of tryptophans



1401, 1424 & 1427
Clues to the structure of Earth's mantle

◩ Indicates accompanying feature

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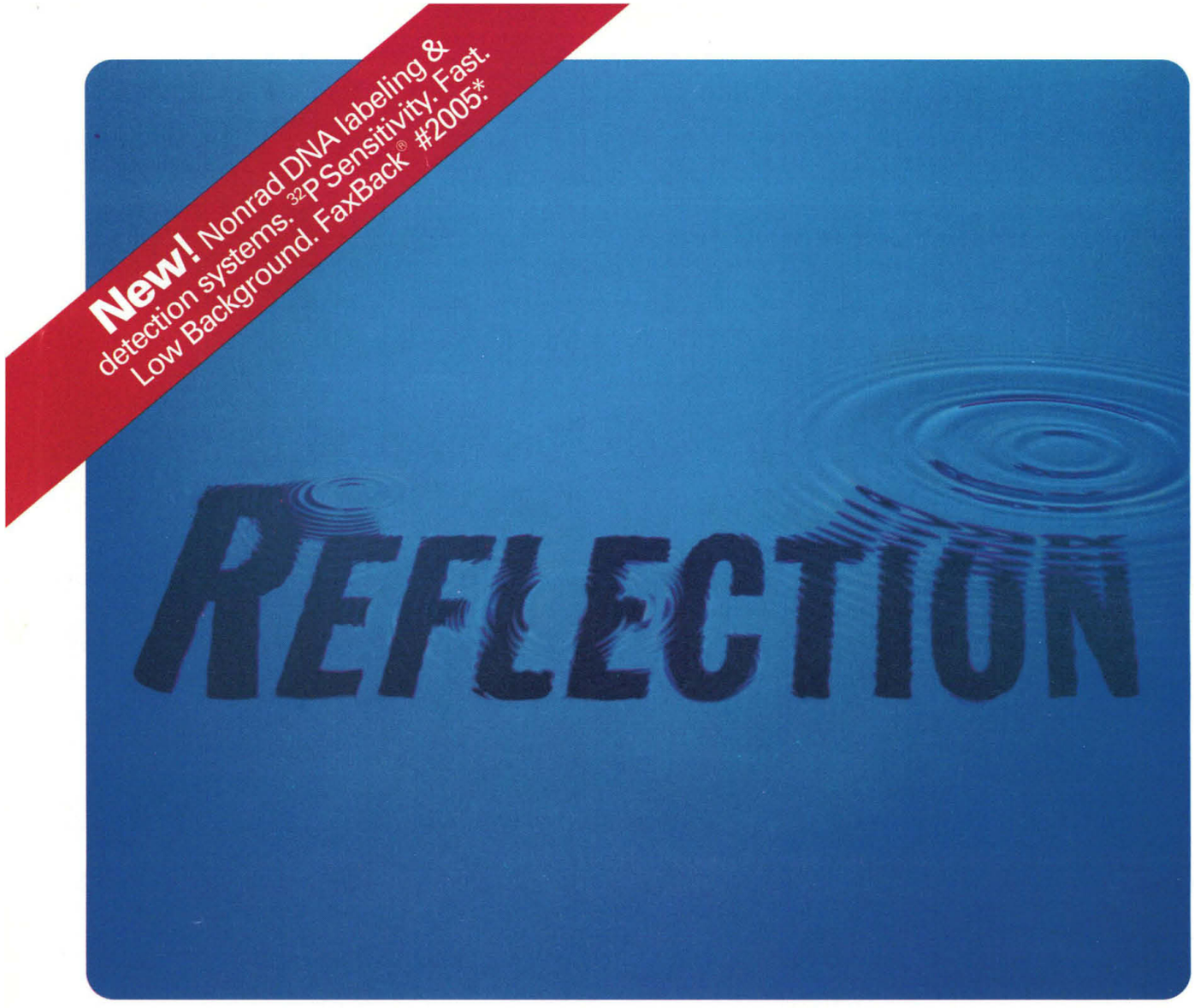

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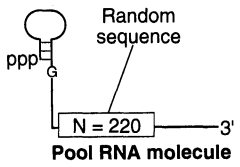
Ribozymes that can catalyze the ligation of two RNA molecules held by a template RNA molecule have been generated through an iterative in vitro selection method. Bartel and Szostak (p. 1411) initially generated a large pool of 10^{15} sequences. Despite this diversity, the number of possible sequences still represents a scant fraction of the sequences possible for the random segment. The catalytic RNA molecules were subjected to further rounds of mutation and selection, which improved the catalytic activity of some of these molecules from a factor of ~10^3 to a factor of ~10^6. In a Perspective, Benner (p. 1402) contrasts the selection and design approaches for developing catalytic macromolecules.



■

Jumping around

An elementary chemical reaction that is run in the dark and that begins and ends in the ground state is normally presumed to have stayed there. Barnes *et al.* (p. 1434) show that in the gas-phase bimolecular reaction of potassium with sodium bromide (K + NaBr), part of the reactive flux spends all of its time in the ground state, but part of the flux hops onto a low-lying excited state for several molecular vibrations and then jumps back to the ground state. This additional thermal energy pathway was deduced from the difference in excitation spectra for the two sodium *D* lines in the laser-assisted reaction.

Background aerosols and polar ozone depletion

In late winter and early spring, the depletion of ozone in the polar stratosphere is usually accompanied by conditions that favor the formation of polar stratospheric clouds (PSCs). The catalytic chemistry of ozone depletion has suggested that type I PSCs, which are thought to be composed of nitric acid trihydrate (NAT), might be essential for the chlorine activation process that generates Cl and ClO. Molina *et al.* (p. 1418) studied the phase relations in the $H_2SO_4/HNO_3/H_2O$ system and show that background H_2SO_4-water aerosols can readily adsorb HNO_3 vapor and grow into PSCs. Also, chlorine radical precursors form readily at polar temperatures (below 200 K) by HCl uptake on liquid H_2SO_4 particles and on solid H_2SO_4 hydrates. These results suggest that PSCs are not essential for chlorine activation, although they provide high surface areas and decrease NO_2 concentrations by scavenging HNO_3.

Kinks in silicon

Pure metals are relatively soft, whereas solids such as silicon are hard and brittle, largely because dislocations in covalent materials are immobile except at high temperatures. However, a proper theoretical explanation for the behavior of dislocations in materials has been lacking. Gilman (p. 1436) offers the analogy of substitution reactions in chemistry: motion of kinks along dislocation lines breaks symmetry, and is therefore forbidden. Moreover, suggests the author, kink mobility may be directly related to electronic structure. This, in turn, influences dislocation velocities and hence, material hardness.

■

No nucleus needed

When cells are exposed to ultraviolet (UV) irradiation, transcription factors such as AP1 and NFκB are activated. It has long been thought that this activation required a nuclear signaling cascade triggered by DNA damage or its by-products. Devary *et al.* (p. 1442) demonstrate that NFκB activation can occur without a nuclear signaling cascade in enucleated cells. Like the UV induction of AP-1, the UV activation of NFκB requires a signaling pathway that involves Src, the Ha-Ras small G protein, and Raf-1.

■

Thwarting viruses with NO

Interferons (IFNs) inhibit virus replication, but the underlying mechanisms remain mysterious. Karupiah *et al.* (p. 1445) have shown that in macrophages, the antiviral effects of IFN-γ are mediated through induction of nitric oxide synthase (NOS) and its product, the multifunctional messenger molecule NO. The antiviral activity associated with NOS may explain why this autotoxic enzyme is so widely inducible.

■

T cell vaccine

Activated autoreactive T cells are often implicated in the induction of autoimmune diseases. In patients with multiple sclerosis (MS), T cells can be found that are reactive toward myelin basic protein (MBP). Zhang *et al.* (p. 1451) used MBP-reactive T cells from MS patients to develop a T cell vaccine. These T cells were cloned, activated, and attenuated by radiation treatment. The clones were then reinjected back into the patients. After the second inoculation, the frequency of circulation MBP-reactive T cells declined notably, and regulatory T cells that inferred with the MBP-reactive T cells could be isolated. This result demonstrates that T cell–mediated autoimmune diseases can perhaps be controlled by giving the regulatory network a boost.

■

Break-in code for entering cells

Mycobacterium tuberculosis, the infectious agent of tuberculosis, escapes the host's immune response in part by entering macrophage cells, where it can survive indefinitely before escaping and proliferating. Arruda *et al.* (p. 1454; see news story by Aldous, p. 1390) have cloned DNA sequences responsible for cell entry and survival. When such sequences were transferred to a nonpathogenic strain of *Escherichia coli*, the bacteria could enter and survive in human HeLa cells.

■

Gramicidin-lipid structure

A high-resolution structure of gramicidin A, a cation channel, in phospholipid bilayers has been determined by Ketchem *et al.* (p. 1457) using solid-state nuclear magnetic resonance spectroscopy. The hydrogen bonds formed by the helical peptide as well as the orientations of the indole side chains of the tryptophan residues can be identified. The tryptophans appear to serve a dual role in anchoring the peptide with respect to membrane and in assisting in the movement of cations.

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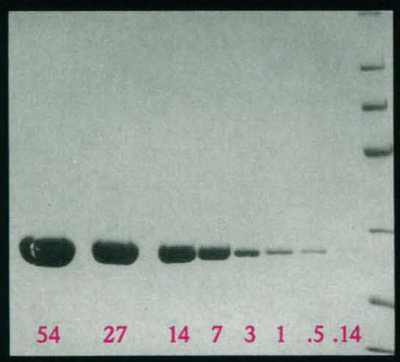

SDS-PAGE of recombinant BamH I restriction endonuclease demonstrating purity of enzyme preparation from the cloned BamH I gene. Lanes represent a 2-fold dilution from 54 to 0.14 µg BamH I per lane. Lane 9 contains molecular weight standards. Molecular weight of BamH I protein = 24,570 daltons. This preparation was used to grow BamH I crystals which led to solving its three-dimensional structure. (A. Aggarwal, personal communication)

62 Recombinant Restriction Endonucleases

Aat II	BspE I	Hind III	Not I
Acc I	BspH I	Hinf I	Pst I
Afl II	Dde I	HinP1 I	Pvu II
Afl III	Dpn I	Hpa I	Sac II
Alu I	Dpn II	Hpa II	Sal I
Ase I	Eag I	Kas I	Sau96 I
Ava I	EcoO109 I	Mbo II	Sfi I
Ava II	EcoR I	Msc I	Sma I
Avr II	EcoR V	Msp I	Sph I
BamH I	Fok I	Mwo I	Sty I
Ban I	Fsp I	Nae I	Taq$^{\alpha}$ I
Bbv I	Hae II	Nco I	Xba I
Bcg I	Hae III	Nde I	Xho I
Bgl I	Hga I	NgoM I	Xma I
Bgl II	Hha I	Nla III	
BsaA I	Hinc II	Nla IV	

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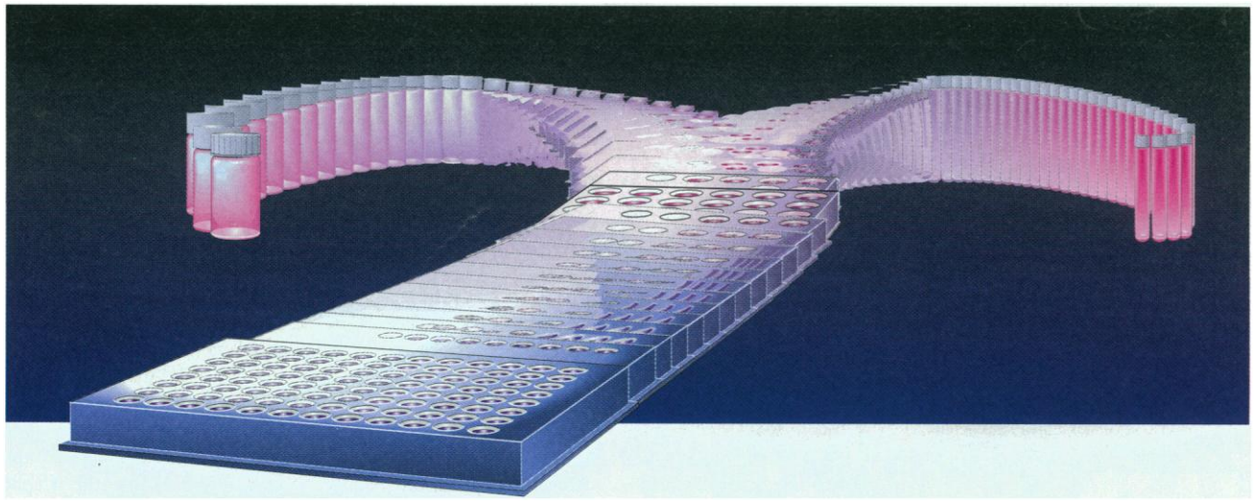

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TopCount can measure radioisotopes in 96- and 24-well microplates, up to 12 wells simultaneously. Reflective optics and proprietary counting technology prevents optical crosstalk and maintains high counting efficiency. TopCount is the first microplate system to offer true LSC performance, including dual label DPM with external standardization.

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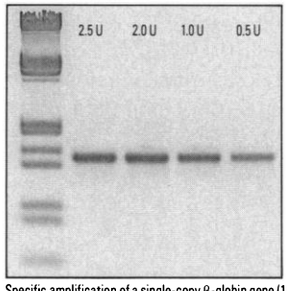

Specific amplification of a single-copy β-globin gene (1.5 kb) from 100 ng of human genomic DNA using various unit (U) quantities of Boehringer Mannheim *Taq* polymerase.

The highest levels of product purity are provided so that you achieve specific, high-yield amplification with no background and no false priming.

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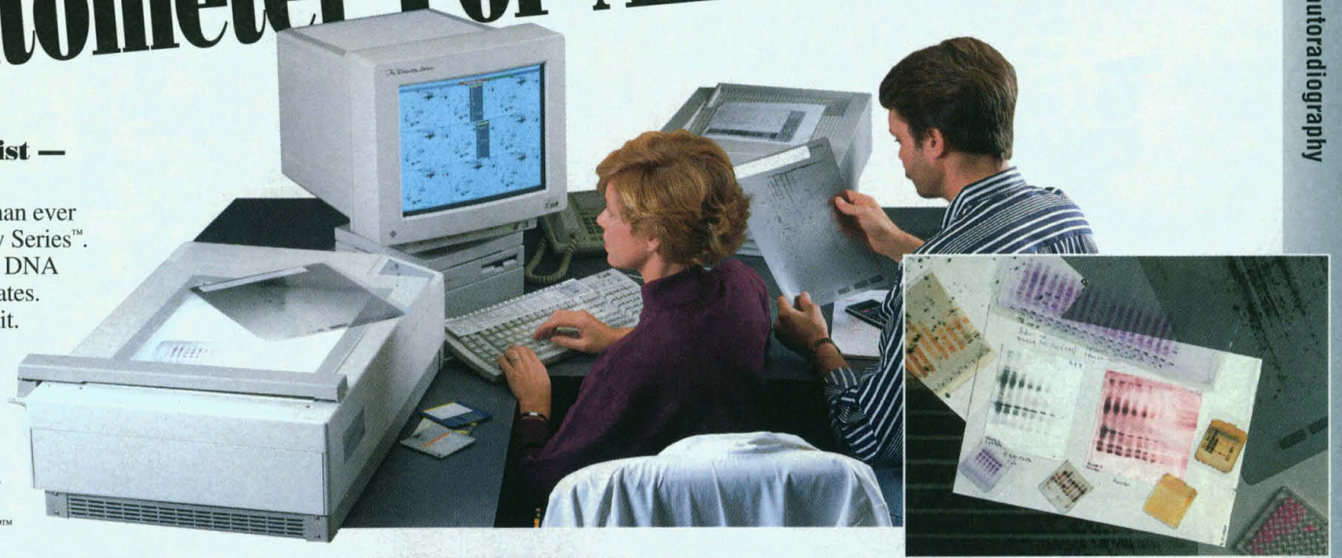

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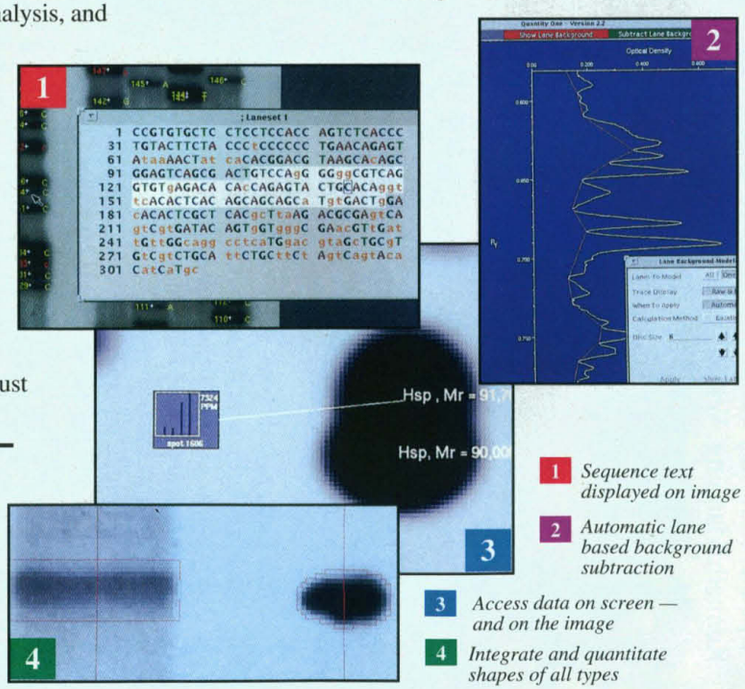
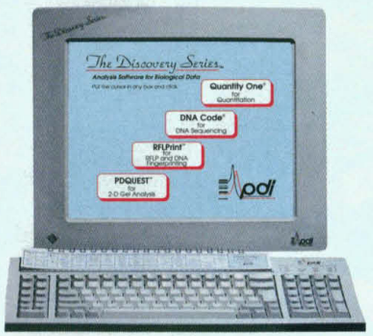


1 *Sequence text displayed on image*

2 *Automatic lane based background subtraction*

3 *Access data on screen — and on the image*

4 *Integrate and quantitate shapes of all types*



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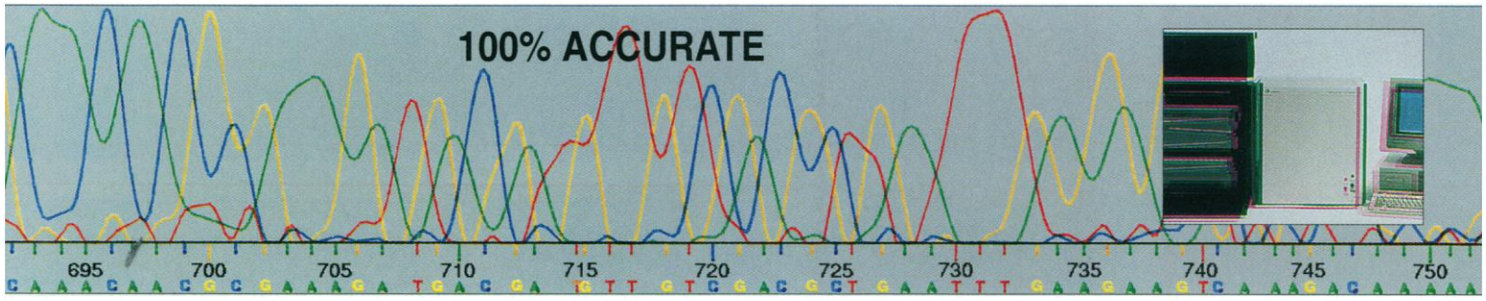

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In another study (4), the leading competitor's DNA sequence error as a function of length increased rapidly from 1% in the 0-350 nucleotide range to about 17% at 500 nucleotides, reaching a plateau of 25% error at 560 nucleotides. Furthermore, to get reliable data, this instrument required a redundancy of 8.4 reads per nucleotide.

In contrast, a standard ALF DNA Sequencer was more than 99% accurate over 500 base pairs and sequenced with a low overall redundancy of 2.8 (one third of the rival sequencer) in the course of the European Community *Saccharomyces cerevisiae* genome sequencing project (5).

1. Data supplied by M. Uhlén and T. Hultman from routine sequencing run at the Royal Institute of Technology, Stockholm, Sweden.

2. Comparison of three non-isotopic aotomated DNA sequence analysis systems. Poster presentation at the *San Diego Conference on Nucleic acids, Nov. 20-22, 1991.* Van Ranst, M., Fiten, P., Voet, M., Volckaert, G., Opdenakker, G.

3. Uniform scoring system for the assessment of DNA sequencing accuracy. *Meth. Mol. Cell. Biol. 3 (1992) 243-245,* Van Ranst, M., Fiten, P., Voet, M., Volckaert, G., Opdenakker, G.

4. Sequence length and error analysis of Sequenase and automated Taq cycle sequencing methods. *BioTechniques 14 (1993) 442-447,* Koop, B.F., Rowan, L., Chen, W.-Q., Deshpande, P., Lee, H., Hood, L.

5. An efficient low redundancy large scale DNA sequencing strategy: Primer walking on plasmid and cosmid DNA using *T7 DNA polymerase* and fluorescein-15*-dATP as internal label. Submitted for publication in *BioTechniques,* Voss, H., Wiemann, S., Zimmermann, J., Grothues, D. Sensen, C., Schwager, C., Stegemann, J., Erfle, H., Rupp, T., Sproat, B., Ansorge, W.

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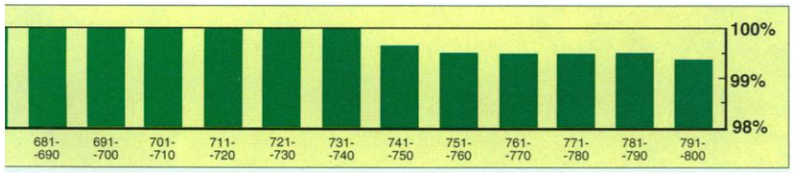

Fully automated base calling from a routine 800 base sequencing run. ALF was 100% accurate up to 740 base pairs (1).

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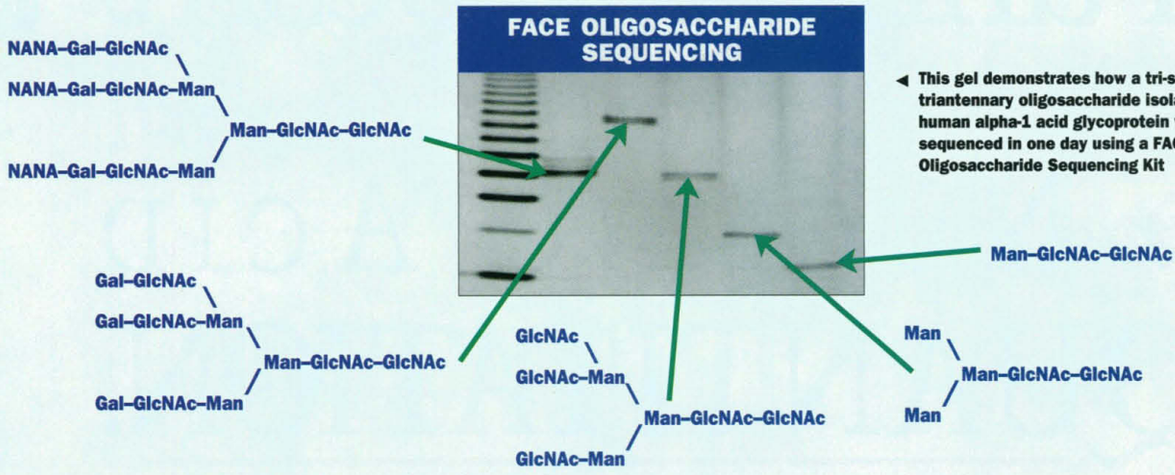
Sequence carbohydrates in one day with Glyko Recombinant Glycosidases



◀ This gel demonstrates how a tri-sialylated, triantennary oligosaccharide isolated from human alpha-1 acid glycoprotein was sequenced in one day using a FACE N-linked Oligosaccharide Sequencing Kit

At last. Fast, simple, and accurate oligosaccharide analysis

No matter what separation technique you employ, Glyko recombinant glycosidases now make it possible for you to sequence oligosaccharides right in your own lab.

The oligosaccharide shown above (lane 2) for example, was sequenced in one day by simultaneous digestion using a series of Glyko enzyme mixtures contained in the FACE® *(Fluorophore Assisted Carbohydrate Electrophoresis)* N-Linked Oligosaccharide Sequencing Kit.

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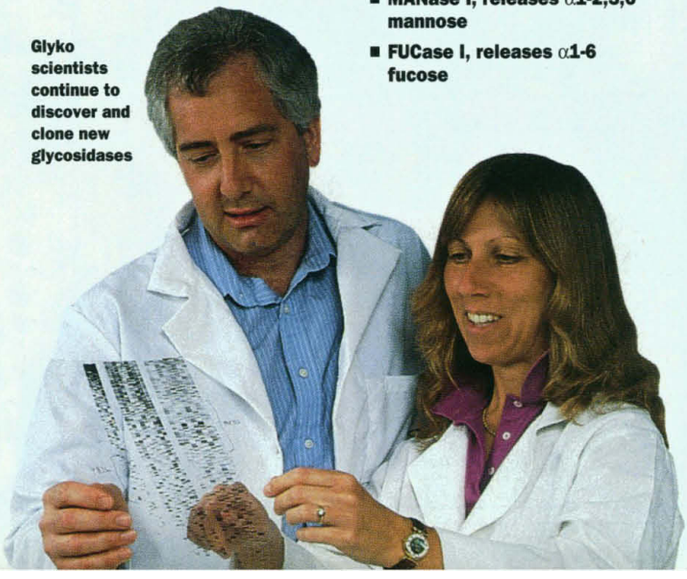
- **NANase III, releases α2-3,6,8 N-acetylneuraminic acid**
- **Neuraminic Acid Linkage Analysis Kit contains NANase I, II, and III**
- **HEXase I, releases β1-2,4,6 N-acetylglucosamine**
- **MANase I, releases α1-2,3,6 mannose**
- **FUCase I, releases α1-6 fucose**



Glyko scientists continue to discover and clone new glycosidases

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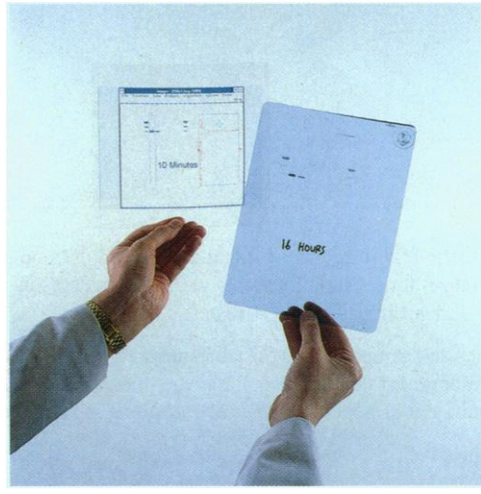
Hard to imagine? Just look at the following example of a Southern blot from Prof. E. Southern's laboratory, University of Oxford, UK. On the right is a conventional X-ray film after a 16 hour exposure.



On the left is the same sample imaged and quantitated with the InstantImager, in just ten minutes.

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