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# Breaking the Mold



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## The Commitment to Discovery

Stratagene is committed to thermostable enzyme research. We literally go to the ends of the earth looking for novel microorganisms which may contain useful thermostable enzymes. Our goal is to make recombinant DNA methodologies more efficient and less time-consuming by exploiting these newly discovered enzymes that excel at elevated temperatures.

## The Results of Our Search

Stratagene's search has been quite fruitful. We have broken new ground with thermostable enzymes isolated from the hyperthermophilic marine archaeon, *Pyrococcus furiosus* (*Pfu*)<sup>1</sup>. This extremely thermophilic microorganism grows optimally at 100°C and as may be expected, possesses a host of exceptionally thermostable enzymes.

Scientists at Stratagene have recently cloned *Pfu* DNA ligase<sup>2,3</sup>, which remains active following one hour incubation at 95°C and functions superbly in the ligase chain reaction (LCR)<sup>4,5</sup>. Cloned *Pfu* DNA polymerase\* exhibits 12-fold higher fidelity than *Taq* polymerase<sup>6,7</sup>. The exonuclease-deficient mutant of *Pfu* DNA polymerase can be used to directly sequence PCR\*\* products with <sup>35</sup>S-dATP<sup>8</sup>.

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### Cloned *Tth* DNA ligase

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## REFERENCES

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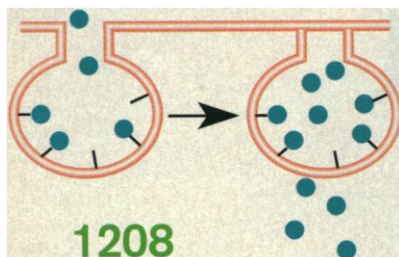
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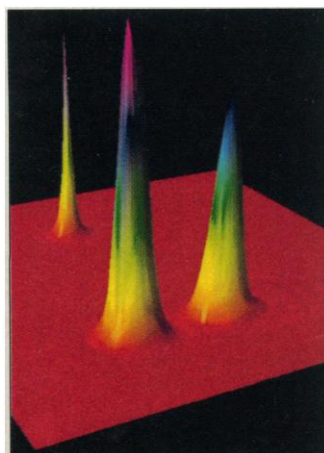
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technological—convene to exchange and publicize new knowledge. See page 1287 for a complete program and registration information. [Earth image: National Aeronautics and Space Administration. Additional illustration: Tracy Keaton Drew, Washington, DC]



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# THIS WEEK IN SCIENCE

edited by PHIL SZUROMI

## Vox pox

Smallpox virus, which requires a human host, has been virtually eradicated. Many people have no immunity against this lethal virus, so should the remaining lab stocks be destroyed as scheduled at the end of this year? Or should they be preserved for future research and in case some virus still survives in the wild? In a pair of Policy Forums, Mahy *et al.* (p. 1223) and Joklik *et al.* (p. 1225) debate this issue.

## Electron ejection

Atoms can be ionized by the photoelectric effect; as the light intensity increases, the probability that an electron is stripped off rises as well. Computer simulations have recently shown that this trend may reverse at very high light intensity, as discussed by Eberly and Kulander (p. 1229). Laser-induced stabilization occurs when the atomic electron's wave function is distorted by the strong electromagnetic field of the light, which in turn alters the ionization rate and decreases the probability of ejection. The authors review the computational results and examine the experimental possibilities.

## Silicon spectra

Bulk silicon cannot emit light by luminescence, but an etched, porous silicon surface can. Does the light come from a chemical species at the silicon surface, or is it enhanced photon emission from small quantum-confined nanoparticles? Wilson *et al.* (p. 1242) addressed this question by carefully precipitating size-selected nanocrystals. Their time-resolved photoluminescence and absorption spectro-

## Helping form an meaningful attachment

Gram-negative bacteria become attached to eukaryotic cells through fibers called pili during the early stages of infection. The assembly of these protein fibers is mediated by chaperone proteins, such as PapD in *Escherichia coli*, which transports pilus subunit proteins such as PapG, an adhesion, to the outer membrane for assembly. Kuehn *et al.* (p. 1234) have analyzed the molecular basis of this interaction. Peptides derived from the carboxyl terminal of pilus subunit proteins bind to PapD and inhibit its chaperone activity. An x-ray structure of a carboxyl-terminal peptide from PapG bound to PapD reveals that binding occurs in an immunoglobulin-like cleft through the interaction of positively charged peptide residues with the arginine-8 and lysine-112 residues of PapD. Mutation of these highly conserved residues in PapD inactivates its chaperone activity in vivo.

scopy measurements offer direct evidence that, like bulk silicon, the nanocrystals behave as indirect band gap emitters, and that quantum confinement is the source of the luminescence.

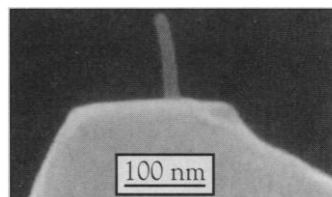
## Single molecule dynamics

Vibrations of a single molecule have been directly observed by Watanabe *et al.* (p. 1244). They used a newly developed femtosecond field emission camera to follow the motion of a single copper phthalocyanine molecule adsorbed onto a tungsten tip. The adsorbed molecule modifies the electron emission properties of the tip as the electrons pass from the metal into the vacuum through the molecule. A modified current is observed that is modulated by the vibrations of the molecule relative to the metal surface.

## Nanowire magnets

Iron filaments less than 10 nanometers in width and hundreds of nanometers in length have been fabricated on silicon substrates. Kent *et al.* (p. 1249) used the scanning tunneling micro-

scope to dissociate gas-phase iron carbonyl. Depending on the bias conditions and pressure,



either relatively pure body-centered-cubic metallic iron or a disordered carbonaceous phase can be formed. Such structures should prove useful in exploring the technological limits of miniaturized magnetic structures.

## Tracking HIV variability

Identifying variant strains of the human immunodeficiency virus (HIV), whether in an infected individual or as the virus moves through a population, is normally a time-consuming, large-scale sequencing exercise. Delwart *et al.* (p. 1257) have developed an assay for variation based on the decrease in gel mobility of DNA heteroduplexes with sequence divergence that arises from gaps and mismatches. The authors use this method to construct a phylogenetic tree relating HIV strains found in different parts of the world.

## Bcl-2 and cell death

Expression of the proto-oncogene *bcl-2* can inhibit apoptosis and necrotic neural cell death, apparently by inhibiting the net generation of oxidative species in the cell. The neural cell line GT1-7 is highly sensitive to toxicity by buthionine sulfoximine (BSO), which depletes cells of reduced glutathione (GSH) that helps protect cells from oxidative injury. Expression of Bcl-2 in these cells lessens BSO toxicity. Although cells expressing Bcl-2 have higher GSH concentrations, Kane *et al.* (p. 1274) show that Bcl-2 still has a protective effect even when GSH is depleted by exposure to diethyl maleate. However, Bcl-2 expression decreases the concentration of hydrogen peroxide and hydroxyl radicals and can rescue yeast mutants lacking superoxide dismutase, an enzyme that protects cells against oxidative damage.

## From start to finish

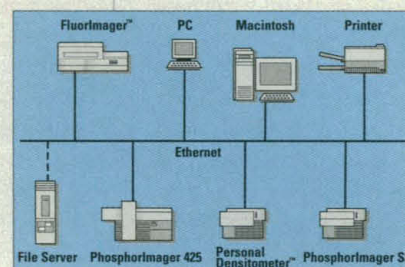
Flagella construction in *Salmonella typhimurium* requires the coordinated regulation of three gene hierarchies; each class of genes is necessary for the expression of the subsequent class. Hughes *et al.* (p. 1277; see the Perspective by Losick and Shapiro, p. 1227) have studied how the cell can detect the synthesis of the initial components of the flagella (hook-basal body complex) and then turn on the late genes to finish the flagella. The intracellular levels of FlgM are regulated in concert with the construction of the flagella. The expression of the late gene class is prevented by a negative regulator FlgM. FlgM is expelled from the cell through an opening in the flagellar hook-basal body complex to allow expression of the late genes.



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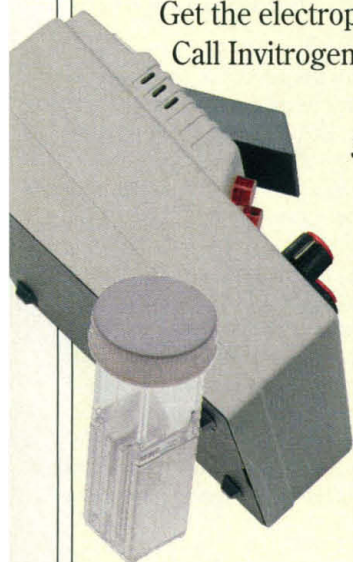
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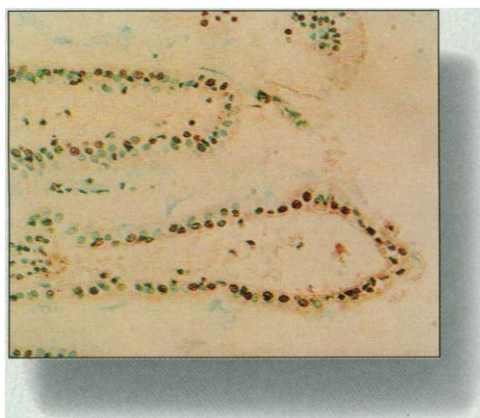
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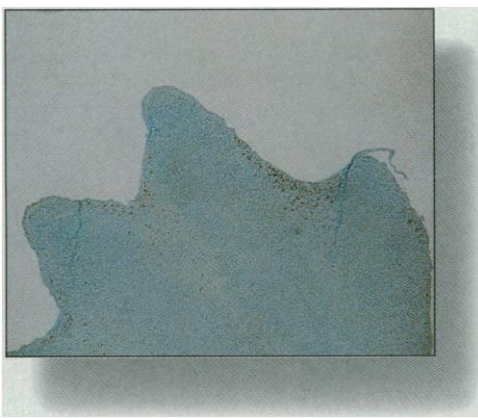


Unlocking the Secrets  
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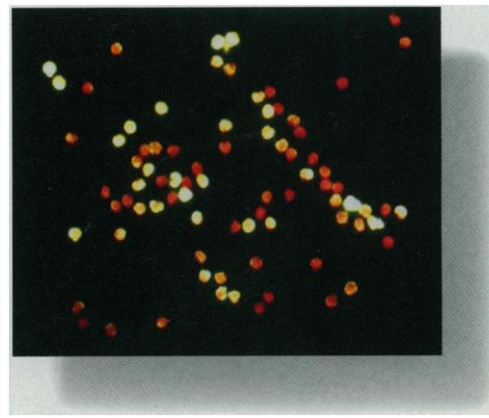
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<sup>1</sup>JFR Kerr, AH Wyllie & AR Currie, (1972) *British Journal of Cancer*; 26:239-257. CS Potten, (1977) *Nature*; 269:518-521.

<sup>2</sup>JFR Kerr, J Searle, BV Harmon & CJ Bishop, in: CS Potten (ed), (1987) *Perspectives in mammalian cell death*.

Oxford U. Press, pp. 93-128. Z Zakeri, D Quaglini, T Latham & R Lockshin, (1993) *FASEB Journal*; 7:470-478; and manuscripts submitted.

<sup>3</sup>X Li, W James, F Traganos & Z Darzynkiewicz, (1993) manuscript submitted.



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## A Technological Advance

How can you maintain healthy animals in a 'Barrier' at cage level and provide Hepa filtered **air** and automatic **water** to each individual cage?

Take the industry approved Micro-isolator™ cage and add to it an air diffuser grommet and bedding proof automatic watering valve. We call this our new Micro-Isolator A/W™ System (Micro Isolator **AIR/WATER** system).

### Background

In 1984 Lab Products, Inc., introduced and patented the Micro-Isolator™ Static Caging System and combined with its Stay-Clean™ Workbench provided the industry for the first time a complete animal

changes can be extended up to two weeks for mice. Eliminate water bottles and save labor with our bedding proof valve! Sterilization is more efficient since the air grommet and water valve, is an integral part of the cage, and is autoclaved with it.

**Equipment and material savings:** With less frequent cage changes (50% or more) the Micro-Isolator A/W means reduced handling of equipment, resulting in less wear and tear on equipment and reduced bedding usage.

most cost efficient and technologically effective methods for protecting your animals.

Now you have multiple solutions for your animal care handling and isolation requirements. You can apply the Original 'classic' Micro-Isolator, or the Micro-Isolator LP™ (low profile) a reduced height version allowing 50% increase rack capacity, the Micro-

Isolator Formed Lid™ which also helps contain bedding material in the cage, and now the Micro-Isolator A/W providing controlled air and water to each cage. A variety of stainless steel rack configurations,

caging and handling system that's providing barrier at cage level, an effective alternative to barrier rooms and their limitations.

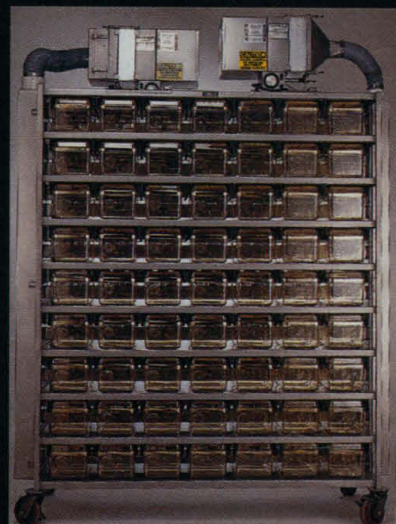
### Benefits of the Micro-Isolator A/W™ System

**Labor savings:** Hepa filtered air introduced to each cage by our unique diffuser grommet provides over 50 changes of air per hour, which dramatically reduces the need for cage changes, new bedding, and sterilization. Cage

**Animal Health:** High ammonia levels have been shown to have serious effects on the animal and research results. With today's costly research animals, sustained healthy environmental conditions are crucial to animal study integrity. With the utilization of Micro-Isolator A/W cage, ammonia, CO<sub>2</sub>, and humidity levels are kept so low, resulting in less stress on animals, improved survival rate of litters, and greater protection against cross contamination.

### A Systems Solution

Lab Products' new generation of Micro Isolator systems combined with our special rack systems and accessories have proved to be the



Micro-Isolator A/W-VCL exhaust rack™ with double sided rack featuring 126 cages, an air supply, exhaust manifold and water line





both open and closed systems provide the ability to integrate these cage systems and provide unparalleled isolation options.

Micro-Isolator A/W systems are so unique they have been granted several U.S. Patents with more pending. Lab products is the only source for these unique products. There are over 1,000 systems in use today.

Other companies have tried to make similar claims but simply do not have the same barrier protection against external and cross contamination.

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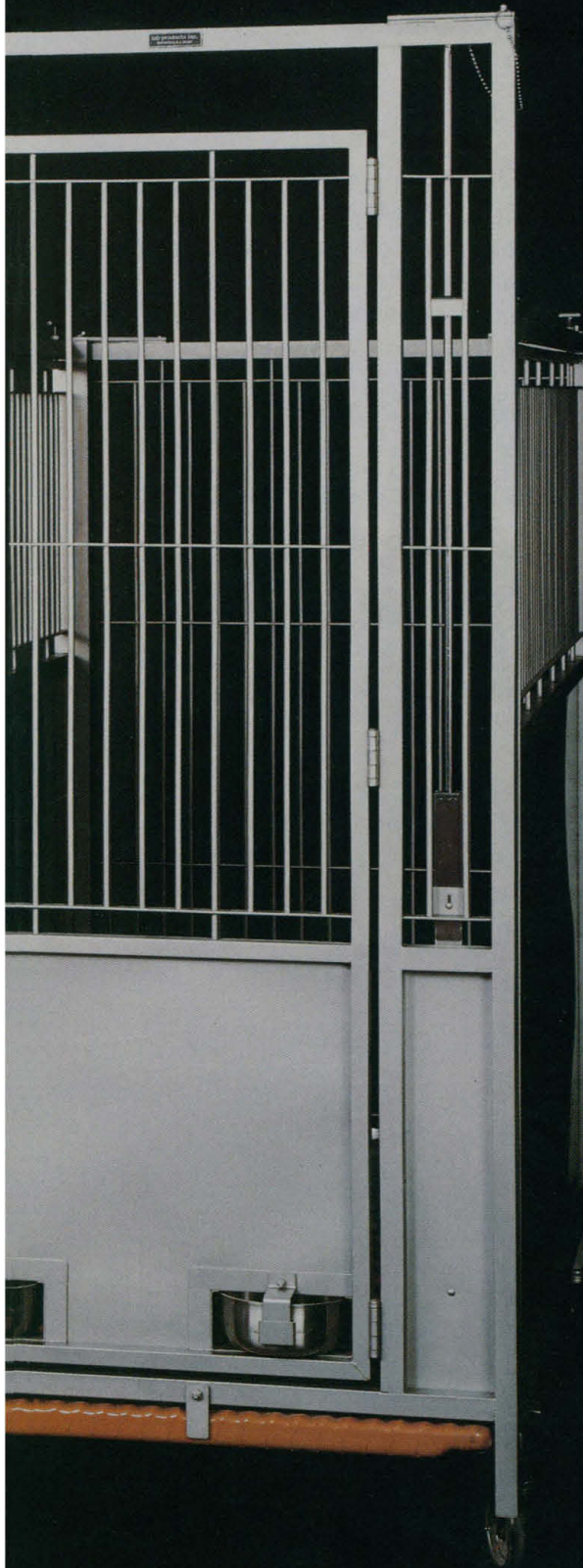
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U.S. Patent Number 5,048,460

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# MOËT HENNESSY • LOUIS VUITTON SCIENTIFIC PRIZE

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## CALL FOR SUBMISSIONS

The LVMH MOËT HENNESSY • LOUIS VUITTON Group announces the 1994 Science for Art Prize

### "UNPREDICTABLE BEHAVIOUR OF MATTER"

This year's Prize would like to stress unpredictable aspects in the behaviour of matter and its manifestations on all imagined or experimental levels. Thus, works in the following scientific fields are particularly relevant **mathematics, physics, chemistry, physical-chemistry** and **biology**, along with all **simulations techniques, analytical tools** or **processes** related with these phenomena.

Priority will be given to those dossiers that deal with **both** aspects, theoretical and experimental or applied.

**Two Prizes, each worth 100 000 FF (equivalent to about US\$ 17,000),** will be awarded

**A Scientific Award** for the scientific study offering the largest field of investigation of fundamental or applied research.

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### Winners of the SCIENTIFIC AWARD

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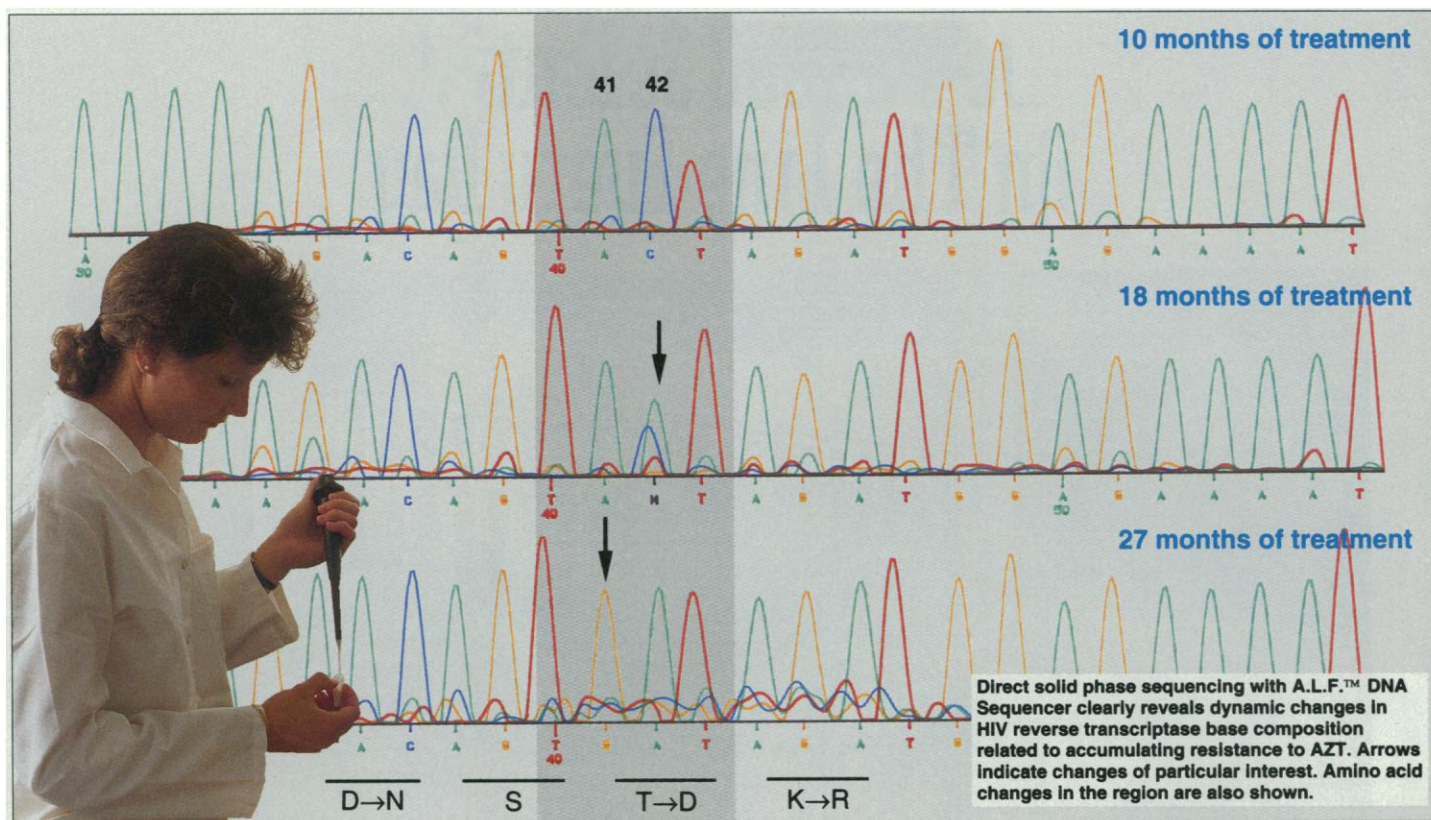
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## A.L.F.™ DNA Sequencer helps AZT fight HIV

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.

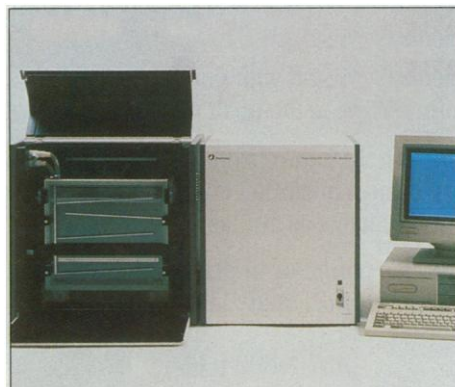
The non-edited data output above shows DNA sequences of HIV RT from a patient undergoing AZT treatment<sup>(1)</sup>. This clean sequence with little background signal emphasizes the suitability of A.L.F. for direct genomic sequencing of clinical samples. Detailed analysis revealed dynamic changes in 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., Lundberg, J., Cox, S., Wahren, B., Uhlen, M.

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# Seeking Information on *Taq* DNA Polymerase

*We are seeking to contact individuals who have knowledge concerning or have used the Kaledin or Chien procedures (Biokhimiya (1980) 45:644-651, Biochemistry (4 Part 1, 1980) 45:494-501; or J. Bacteriology (1976) 127:1550-1557) at any time prior to December, 1989, whether in research or practice.*

*We are also seeking to contact individuals who have any knowledge of any company, researcher or institution who may have experience purifying Taq DNA Polymerase prior to December, 1989.*

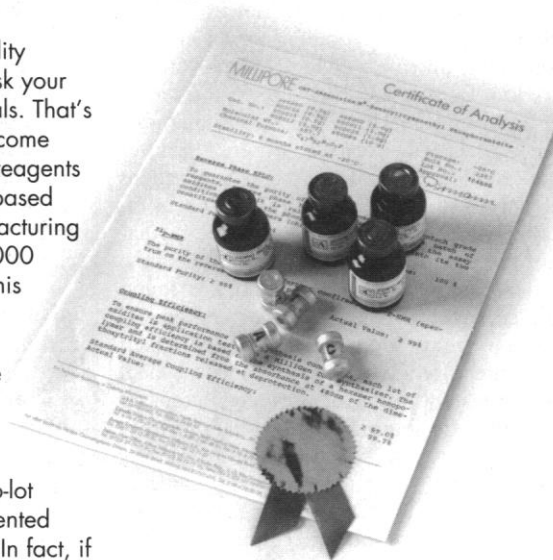
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