INDUSTRIAL POLICY

# New Program Funds Genome Technology

The human genome project is still years from its goal of mapping and sequencing the entire human genetic code, but the disease-related genes it has already turned up are forcing planners to prepare for the next step— widespread genetic testing and diagnostics. The problem is that testing for a single gene can cost more than a hundred dollars—a factor of 10 or more too expensive for widespread use. Better technology is the answer, say planners, but industry is often reluctant to spend money before a market has developed, and the genome project's $30-million annual budget for technology is focused on sequencing, not diagnostics. Enter the Commerce Department.

Last week, the department announced a 5-year, $145-million program of competitive awards to industry to develop DNA diagnostic technology for the commercial market. The DNA initiative is one of five new research areas receiving a total of $745 million as part of the department's Advanced Technology Program (ATP). Additional program areas will be selected later in the year. The genome project's two backers, the National Institutes of Health (NIH) and the Department of Energy (DOE), will help ATP choose the awards, and officials from both agencies expect the technologies developed under the ATP program to aid the genome project as well.

ATP, housed within the National Institute of Standards and Technology (NIST), provides government support for research projects led by industry that have not yet generated a marketable product (*Science*, 25 March, p. 1676). Its early awards were spread across dozens of fields, but an influx of new money—its budget tripled this year to $200 million, and the administration has pledged to raise it to $750 million by 1997—led NIST to concentrate most of its budget in a handful of fields where its efforts could have the most impact. NIST expects that grants from the program, to be awarded by the end of September, will be matched by equal funding from industry.

The DNA diagnostic effort, says NIST program director Stanley Abramowitz, will attempt to foster innovative technologies that are high-risk and high-payoff. Among the technologies ATP will consider are DNA-screening chips, robotics, better fluorescent dyes, and ways of running DNA processes in parallel. The goal, he says, is to find technologies that apply the power of genetic screening not only to humans, but also in plant breeding, animal husbandry, environmental monitoring, and industrial biomanufacturing.

One approach uses a chip-based hybridization method, in which thousands of short DNA sequences are placed on a silicon substrate, similar to a computer chip. When a DNA sample is flowed over the chip, the sequences that match those on the silicon hybridize, leaving fluorescent markers that can be detected with lasers or generating an electrical signal through the chip itself. A chip could be loaded with sequences of all the known mutations that cause cystic fibrosis, for example.

The concept of such detection methods isn't new, says Stephen Fodor of Affymetrix, a Santa Clara, California, company that is researching DNA chips and intends to compete for an ATP grant, but key elements of the technology—such as converting the hybridization into a coherent electric signal—are still unproven. ATP's program, he says, encourages innovation in advance of the time when the genome project will create a demand for widespread genetic testing. For example, Fodor says an ATP grant would help Affymetrix design a one-stop diagnostic—a credit-card sized device that could both amplify DNA and screen it.

The ATP funding could also benefit the genome project itself, says Robert Strausberg, director of the technology development program at NIH's National Center for Human Genome Research. For example, NIH-funded efforts to reduce the cost of full-genome sequencing through sequencing by hybridization could use the same technology as the DNA diagnostic chips ATP hopes to support. Another technology is micro-machining the DNA amplification and handling processes, which could reduce the amount of reagents—the most expensive part of both sequencing and genetic diagnostics—by a factor of 100.

ATP will launch similar 5-year research programs in four other areas: new information systems for health care, cheaper ways to manufacture composite materials, computer-integrated manufacturing for electronics, and research on component-based software. The last category is an attempt to create ways to write software without the laborious "hand-assembly" now required, says NIST program manager David Fisher.

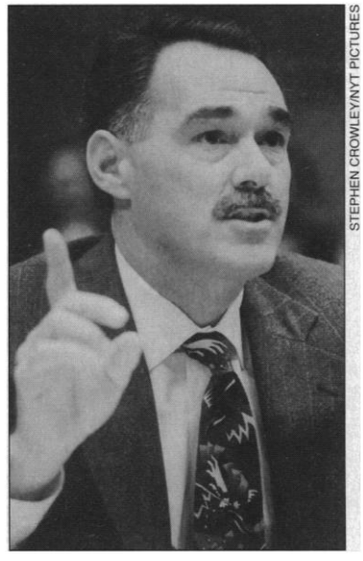
**–Christopher Anderson**

TOBACCO INVESTIGATION

# Was Safer Cigarette Research Snuffed?

Rose Cipollone died of cancer because she smoked, according to a 1988 court verdict against the tobacco companies Liggett, Lorillard, and Philip Morris. In the end, Cipollone's family never recovered any damages for her death. But the verdict did have some ramifications: Its prospect may have killed a Philip Morris research project to develop a safer cigarette. That's the connection alluded to last week by Representative Henry Waxman (D–CA) after his health subcommittee heard testimony from Victor DeNoble, a behavioral pharmacologist who worked for Philip Morris until 1984. DeNoble testified that his supervisors stopped his research because it was "generating data that could be dangerous to the litigation that was going on at the time."

DeNoble, who now works as a behavior analyst at Delaware Health and Social Services, and another ex–Philip Morris researcher, Paul Mele, now of the Armed Forces Radiobiology Research Institute in Bethesda, Maryland, made these allegations to the subcommittee of the House Energy and Commerce Committee on 28 April. DeNoble said that in 1984 the tobacco company halted his work on nicotine analogs that seemed free of side effects that may exacerbate heart disease among smokers. In an interview with *Science*, DeNoble said that Philip Morris' unease stemmed from evidence produced during this research that cigarette smoke may have addictive effects, and that the order to stop came just months after the Cipollone case began. In addition, DeNoble and Mele told the hearing that Philip Morris forbade them to tell other researchers about evidence suggesting that acetaldehyde, a component of cigarette smoke, enhanced nicotine's addictive qualities.



STEPHEN CROWLEY/NYT PICTURES

**Smoking gun?** Victor DeNoble says his findings about nicotine and addiction worried his tobacco company bosses.

Philip Morris senior vice president Steve Parrish admits that the company prevented the researchers publishing some of their findings, but specifically disputes any connection between the Cipollone lawsuit and Philip

Morris' research decisions. "The Cipollone case was filed in August 1983, and the lab wasn't closed until sometime in the spring of 1984," he says. "It just doesn't make any sense" to connect the two events.

It does to DeNoble. He, Mele, and other Philip Morris researchers had discovered in 1983 that rats responded to two synthetic analogs of nicotine, 2' methyl nicotine and 4' methyl nicotine, as if they were the real thing: When the rats received an injection of any of the three substances directly into the brain, they became temporarily limp and floppy. And after being trained to push a specific lever upon receiving a subcutaneous nicotine injection, the rats would also push that lever after injection with the analogs, but not with other substances.

There was, however, one crucial difference between the analogs and the original: A test showed the analogs, unlike nicotine, didn't have the ability to trigger smooth and cardiac muscle contraction. By stimulating smooth muscle lining the blood vessels, as well as the heart, nicotine boosts both blood pressure and heart rate. This increases the likelihood of heart attacks in people with a pre-existing cardiac condition, says Neal Benowitz, a nicotine expert at San Francisco General Hospital. DeNoble told the subcommittee that Philip Morris wanted to develop a cigarette that had no effect on the cardiovascular system, but still had nicotine-like effects on the brain that made smoking pleasurable. But the line between pleasure and addiction had company officials worried, DeNoble said.

DeNoble and Mele's second unpublished discovery probably worried them more. The two researchers showed that rats will push levers 100 times per day to inject nicotine or acetaldehyde into their veins at concentrations roughly equivalent to that found in cigarette smoke. When offered acetaldehyde and nicotine together, the rats quadrupled their efforts, pushing the levers 500 times per day.

Both of these findings, however, have other addiction researchers rather confused at the moment. According to Benowitz, for example, recent studies suggest that increased blood coagulation, not vasoconstriction, is mainly responsible for the increased incidence of heart attack and stroke among smokers, and that such coagulation is caused by an unidentified substance in cigarette smoke. As for acetaldehyde, Paul Kulkosky, an alcohol addiction expert at the University of Southern Colorado, notes that most addiction researchers believe that the substance, a breakdown product of alcohol, is far too rapidly metabolized to create any dependency. Nonetheless, says Kulkosky, "it's a provocative finding" that needs looking into.

DeNoble told the committee he never had the chance to explore these questions any further. In April 1984, he testified, he was told by his supervisor that animal experiments must stop forthwith. "I was told to shut the equipment off and kill all the animals," said DeNoble. "The lab was over, ended."

Parrish refuses to comment on DeNoble's acccount of the lab shutdown. But, he says, "we are investigating what happened in 1984." According to Parrish, Philip Morris intends to furnish Waxman's subcommittee with "documents we have regarding DeNoble's research" by 9 May. Meanwhile, the charges have made an impression on Food and Drug Administration commissioner David Kessler, who contends that cigarettes should be regulated by his agency if manufacturers intend nicotine to be used as a drug to satisfy an addiction. DeNoble and Mele's testimony, said Kessler in a written statement, "paints a picture of an intensive and sophisticated research program concerning the addictive potential of nicotine."

–Rachel Nowak

## NAS Elects New Members

Last week, the members of the National Academy of Sciences elected nine women and 51 men to join their elite ranks. Fifteen scientists were elected as foreign associates.

The new members are:

**Eric G. Adelberger**, University of Washington; **Sankar Adhya**, National Cancer Institute; **Frederick W. Alt**, Howard Hughes Medical Institute, Harvard Medical School; **Frederick M. Ausubel**, Harvard Medical School, Massachusetts General Hospital; **Mary Ellen Avery**, Harvard Medical School; **May R. Berenbaum**, University of Illinois, Urbana-Champaign; **Spencer J. Bloch**, University of Chicago; **Henry R. Bourne**, University of California, San Francisco; **William S. Bowers**, University of Arizona; **Marvin H. Caruthers**, University of Colorado; **Donald L.D. Caspar**, Brandeis University; **Leroy L. Chang**, Hong Kong University of Science and Technology; **Arnold L. Demain**, Massachusetts Institute of Technology; **Stanley Deser**, Brandeis University; **Gerald D. Fasman**, Brandeis University; **Alfred G. Fischer**, University of Southern California; **John H. Flavell**, Stanford University; **Marye Anne Fox**, University of Texas at Austin; **Michael Freeling**, University of California, Berkeley; **David V. Goeddel**, Tularik Inc., South San Francisco.

**Eville Gorham**, University of Minnesota; **John P. Hirth**, Washington State University, Pullman; **James R. Holton**, University of Washington; **David E. Housman**, Massachusetts Institute of Technology, Massachusetts General Hospital; **Roger Howe**, Yale University; **Rudolf E. Kalman**, University of Florida, Swiss Federal Institute of Technology, Zurich; **Charles D. Keeling**, Scripps Institute of Oceanography; **Sung-Hou Kim**, University of California, Berkeley; **Judith P. Klinman**, University of California, Berkeley; **Herwig Kogelnik**, AT&T Bell Laboratories, Holmdel, N.J.; **Robert B. Laughlin**, Stanford University; **Anthony P. Mahowald**, University of Chicago; **Andrew J. Majda**, Princeton University; **Pamela A. Matson**, Ames Research Center, National Aeronautics and Space Administration, Moffett Field, Calif.; **Thomas J. Meyer**, University of North Carolina at Chapel Hill; **Albert I. Meyers**, Colorado State University; **David R. Nelson**, Harvard University; **Eugene W. Nester**, University of Washington; **Roger A. Nicoll**, University of California, San Francisco; **Maynard V. Olson**, University of Washington.

**Donald W. Pfaff**, Rockefeller University; **William H. Press**, Harvard University; **Julius Rebek Jr.**, Massachusetts Institute of Technology; **Matilda W. Riley**, National Institute of Aging, NIH; **Michael G. Rosenfeld**, Howard Hughes Medical Institute, University of California, San Diego; **John M. Rowell**, Conductus Inc., Sunnyvale, Calif.; **Jeremy A. Sabloff**, University of Pittsburgh; **Myriam Sarachik**, City College of New York; **Lucille Shapiro**, Stanford University School of Medicine; **Burton H. Singer**, Yale University School of Medicine; **Steven M. Stanley**, Johns Hopkins University; **Edward M. Stolper**, California Institute of Technology; **Stanley J. Tambiah**, Peabody Museum of Archeology and Ethnology, Harvard University; **Thomas N. Taylor**, Ohio State University; **George Veronis**, Yale University; **Ellen S. Vitetta**, University of Texas Southwestern Medical Center; **Eric F. Wieschaus**, Princeton University; **Oliver E. Williamson**, University of California, Berkeley; **Robert B. Wilson**, Stanford University; **Henry T. Wright**, University of Michigan.

Foreign associates:

**Per Oskar Andersen**, University of Oslo (Norway); **George K. Batchelor**, Cambridge University (U.K.); **Alan Carrington**, University of Southampton (U.K.); **Te-Tzu Chang**, International Rice Research Institute, Los Baños, Philippines (Taiwan); **Claude Cohen-Tannoudji**, College de France (France); **Paul J. Crutzen**, Max Planck Institute for Chemistry, Mainz, Germany (Netherlands); **Klaus Hahlbrock**, Max-Planck-Institut für Zuchtungsforschung, Köln (Germany); **Lanpo Jia**, Institute of Vertebrate Palaeontology and Palaeoanthropology, Academia Sinica (China); **Kyoshi Mizuuchi**, National Institute of Arthritis, Diabetes and Kidney Diseases, NIH (Japan); **Salvador Moncada**, Wellcome Research Laboratories (U.K.); **Norman Myers**, development consultant (U.K.); **Sergei P. Novikov**, L.D. Landau Institute of Theoretical Physics (Russia); **Klaus Rajewsky**, University of Cologne (Germany); **Stuart Ross Taylor**, Australian National University (New Zealand); **Anne M. Treisman**, University of California, Berkeley (U.K.).