

## Institutional Profile

# Manifest Destiny at the Scripps Research Institute

*Bolstered by industrial funds, Scripps has expanded into unique territory on the frontiers of biology and chemistry*

**La Jolla**—IN 1986, WHEN THE TOTAL OF its grants from the National Institutes of Health (NIH) passed the \$39 million mark, the Scripps Research Institute began billing itself as the nation's largest "independent, nonprofit biomedical research center." The unspoken rival Scripps had surpassed was the Mayo Clinic. Now, 5 years later, the budget of Scripps—known until 1 July as the Research Institute of Scripps Clinic—has grown to \$85 million, \$58 million of it from NIH. Few people on this campus stretched along the cliffs above the Pacific still mention the Mayo Clinic as an apt comparison. What is?

"Well, that's a hard one," replies Richard Lerner, the 51-year-old director who took over in 1987 from his mentor Frank Dixon, the institute's founder. "But I'd like to see you say Bell Labs. The Bell Labs of chemical biology."

Lerner's ambitious choice of peers—AT&T Bell Laboratories has a staff of 4000 scientists, compared to 170 at Scripps—is consistent with his own drive, which has kept Scripps expanding at a heady pace when many institutions, fraught with funding or leadership uncertainties, are retrenching. And the comparison is not as outlandish as it may seem. Both institutions offer their researchers enviable technical resources and a remarkable degree of freedom. And both have tight links with industry. A decade ago, while most other nonprofit research institutions

and universities were debating the propriety of industrial ties, Scripps raised some eyebrows by embracing a unique long-term licensing agreement with Johnson & Johnson (J&J) that gives the pharmaceutical company first rights to results from Scripps' research. The shell of industrial funds that now surrounds the vulnerable soft-money heart of the operation has encouraged Scripps to develop unique research strengths

at the border between biology and chemistry. And it has helped give the institute what Gerald Edelman of Rockefeller University, who heads Scripps' Board of Scientific Governors, calls "an air of extraordinary optimism in times that put a big strain on optimism."

The results of this synergy of money and vision include the solution of the three-dimensional structure of poliovirus by James Hogle's team; Jeffrey Skolnick's computer algorithm for determining a protein's three-dimensional structure from its sequence; Ian Wilson's findings on the structure of the antigen-antibody complex and how it touches off other immune responses; and Lerner's own work on antibodies with catalytic abilities. And today, in a time of tight federal research budgets, a relationship that once appeared unseemly to some scientists is more likely to be perceived as enviable.

Some of that envy has been of the negative kind, excited by images—sometimes

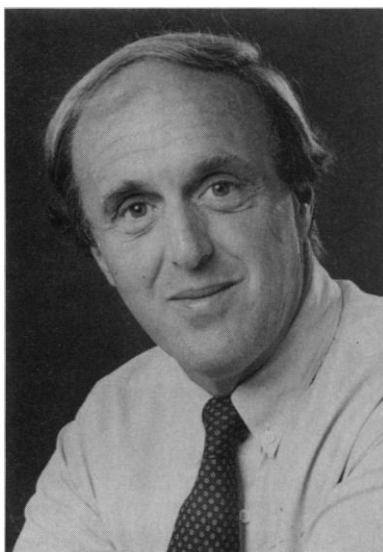
quite exaggerated—of lavishly equipped laboratories and high salaries. And envy has shifted to irritation, for some scientists outside the institute, when Scripps' industrial ties seemed to be getting in the way of data sharing. To protect the interests of its industrial partners, Scripps won't share some materials unless recipients agree to yield to the institute first rights to license any improvements or products developed from them. That practice, which the institute staunchly defends, prompted an outcry last year when university scientists felt Scripps was not giving them full access to a new technology for producing highly specific antibodies in bacteria (see *Science*, 25 May 1990, p. 952).

In spite of such complaints, however, "right now most people would love to use Scripps as a model," according to Peter Schultz of the University of California at Berkeley, a cordial competitor of Lerner's in pioneering the field of catalytic antibodies. "If I could reproduce the J&J deal Lerner has here, I'd do it. It's an example of what a lot of people argue there should be more of."

To Bruce Stillman, assistant director of Cold Spring Harbor Laboratory, Scripps exemplifies the kind of "innovative funding" arrangements that are becoming an economic necessity. "If private research institutes want to remain the best that they can be, we're going to have to investigate ways of cooperating with industry," he says.

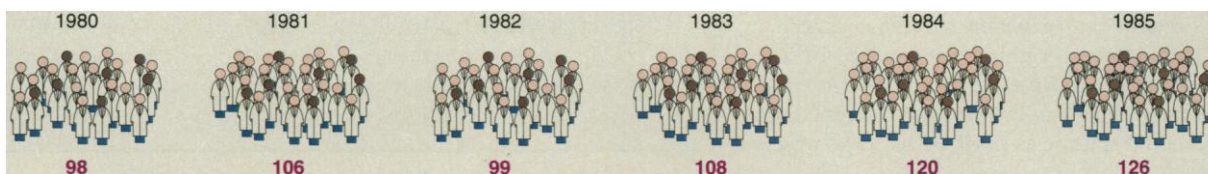
Lerner himself prefers to play down the importance of industry funds, pointing instead to recent successes in getting major private gifts: \$3 million from philanthropist Lita Annenberg Hazen, \$5 million from the Markey Foundation, and \$3 million from the Keck Foundation, among others.

But the present form of Scripps owes much to industrial ties. For the first 20 years after founder Dixon abandoned academic medicine at the University of Pittsburgh School of Medicine in 1961 to start a research department at the small but "genteel" Scripps Clinic in La Jolla, the research institute subsisted almost entirely on NIH funds and pursued research mostly on immunology. But by 1980 Dixon recognized a turning point. "Immunology was absorbing new technologies from molecular biology," he recalls. He considered it critical to propel the institute into molecular biology.



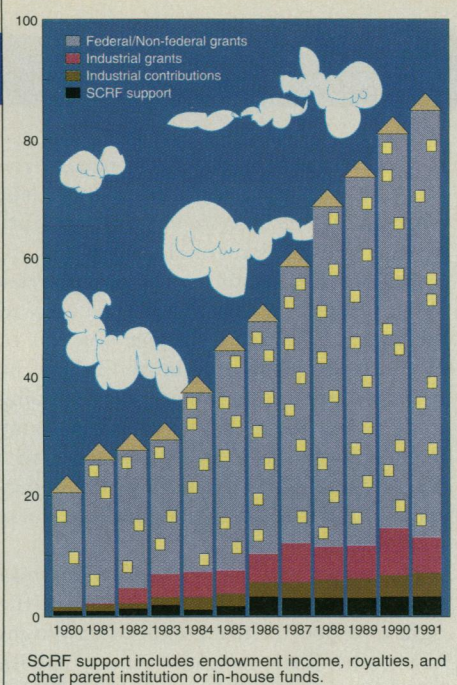
**Outspoken.** *Scripps director Lerner.*

**Steady growth.** *The expansion of the Scripps faculty over the past decade.*





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**A solid foundation.** Industry money as a proportion of the Scripps budget, in millions.

But by then NIH funding was plateauing, and the institute's labs were full. "We had no hard money, no endowment, and the medical end of this operation has always been a financial drag," Dixon says.

So in 1982, for the price of a new molecular biology building and an ongoing financial commitment that today amounts to more than \$10 million a year in grants, contributions, and patenting costs, J&J claimed first rights to license any advances in human and animal health care discovered by Scripps' scientists. The size of the building was doubled in 1985 when Scripps formed a second long-term affiliation, with PPG Industries. PPG now holds first rights to everything in areas not tied up by J&J, such as plant molecular biology and polymer chemistry, and second rights to health care advances J&J doesn't take.

Although industry-university ties are common now, the J&J and PPG affiliations remain unique. "I'm not aware of any others this broad in scope that encompass a whole institution," says Martin Rachmeler, technology transfer director at the neighboring University of California, San Diego, and president of the Association of University Technology Managers.

Scripps is set apart from other research institutes not just by some of its funding arrangements but by how it chooses to

spend the funds. In explaining Scripps' distinctive approach, Lerner resorts again to Bell Labs. The "intellectual currency" of both institutions, he believes, is "the ability to put together critical mass to attack very large and important problems." Lerner admits that focusing resources narrowly is a high-risk strategy. "Critical mass cuts both ways," he says. "Someone could say, 'All that chemistry at the expense of developmental biology? What a dumb way to go.' Whereas, if you take the Noah's Ark approach like a university and hire two of everything, you can't make very big mistakes."

In choosing targets for that critical mass, Lerner is perfectly happy to ignore traditional boundaries between disciplines. It's a pattern he's followed for years. When Scripps created its department of molecular biology in 1983, it picked Lerner, a former Dixon postdoc who was then on the immunology faculty, to head it. Lerner—persuasive, impatient, strong-willed, and, to some, abrasive—eschewed the usual emphasis on gene expression and almost immediately set about laying the foundations for a marriage of chemistry and biology.

Lerner's first push was in structural biology, which focuses on the detailed structures of biological molecules, determined through nuclear magnetic resonance (NMR) and x-ray studies and computer modeling. Today the icons of Scripps' commitment to structural biology preside over the central gallery of the Molecular Biology Building: a new Cray Y-MP supercomputer at one end and giant images of molecular models lining the walls. More recently Lerner has been encouraging forays into bioorganic synthetic chemistry, focusing on the synthesis of large, biologically important molecules.

Many of Scripps' biggest scientific contributions, such as catalytic antibodies, have emerged from these cross-disciplinary enterprises. And the freedom to follow promising research avenues no matter what disciplinary boundaries they cross has served as a powerful lure for new faculty.

"What attracted me was Lerner's vision that we could bring in people at the cellular level—people working in what we consider the major areas of complexity in biology: structures related to the nucleus, membrane trafficking, the cytoskeleton, channels—and

let them interface with those doing structural analysis on proteins at atomic levels of resolution," says Norton B. Gilula, who joined Scripps in 1986 and is chairing a new cell biology department starting this month.

Other recent successes from Lerner's aggressive recruiting efforts echo Gilula's sentiments. K.C. Nicolaou, recruited in 1989 from the University of Pennsylvania to start a new chemistry department, saw at Scripps "a chance to build something we couldn't do anywhere else, without the old-fashioned boundaries that separate disciplines." He immediately set about building a program in bioorganic synthesis that already has made Scripps a leader in the field.

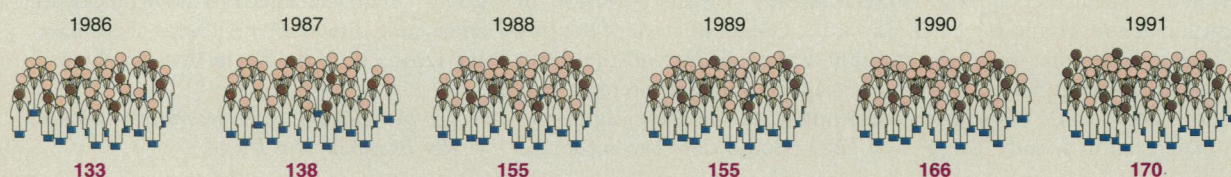
When steering Scripps into new areas, Lerner has tended to recruit from the top down, bringing in big names first. That pattern is continuing. Roger Beachy, one of the nation's top plant molecular biologists, is arriving this month from Washington University to lead a major expansion into that field. Also this summer, Sydney Brenner will begin splitting his time between the Medical Research Council in Cambridge, England, where he has worked since 1957, and a new lab at Scripps, where he will be the focus of a new molecular genetics group.

In spite of this top-down approach, Lerner has weaned Scripps away from its old habit of bringing in young investigators under the wing of senior faculty, European style. Young investigators still tend to arrive after the big names, but they often get their own labs and startup funds. Lerner has also launched two graduate programs. The first, with the unwieldy title of Macromolecular and Cellular Structure and Chemistry, opened in 1989. The second, a program in chemistry with an emphasis on bioorganic synthesis, will take its first class next fall. In 5 years, the programs will add 100 students to Scripps' complement of 170 faculty and 360 postdoctoral fellows.

Topflight faculty and graduate students don't come cheap. Scripps' track record in faculty recruiting has occasionally prompted rumors that the La Jolla institute was dangling outlandish salaries, perhaps even free houses. But associate director William Beers says Scripps' salary scale—although more like the pay scale of medical schools than of academic basic science departments—is not

extravagant. And he flatly denies the institute has ever bought anyone a house.

Lab startup





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funds, which come from Scripps' pool of industrial and private contributions, are a different matter. "The support up front is incredible," says Ronald Milligan, who believes the electron microscope and computerized image-processing equipment he received when he was recruited into the molecular biology department 4 years ago "would take you years to get in a university." Likewise, to bring in Nicolaou, Scripps agreed to provide his new department with extensive core facilities for NMR, mass spectrometry, x-ray crystallography, and computerized molecular modeling.

But after the startup funds are gone researchers at Scripps must get grants to survive, just like their peers at other nonprofit institutes such as Cold Spring Harbor Laboratory and the nearby Salk Institute. Two-thirds of the research operation runs on peer-reviewed NIH grants. Peter Wright, who succeeded Lerner as chairman of molecular biology, believes the industrial money would be wasted if it were used for day-to-day operations. The funds are best used, he says, to "give us the freedom to recruit, to build, to expand, to remain state-of-the-art in instrumentation."

One downside of this arrangement is the envy it elicits among established researchers

section when people are scoring proposals."

Do Scripps' ties to industry have other drawbacks? Do they shape, subtly or overtly, the nature of the institution's research? Berkeley's Schultz believes "that's clearly not the case at Scripps, not at all." Stanford molecular biologist Paul Berg, who has complained in the past about Scripps' restrictions on data sharing, has no gripes about the caliber of the science there. "All in all," he says, "they're certainly a first-class place and one of the leaders in the world in the structural analysis of macromolecules."

Lerner, not surprisingly, believes scientific freedom and industrial sponsorship coexist comfortably at Scripps. "We would like to do something practical," he admits. "We're not unaware of the fact that there could be financial gains. Who's kidding whom? But we never make decisions on that basis. I don't care if K.C. Nicolaou never makes a drug as long as he does good chemistry." Practical applications, Lerner maintains, take care of themselves. "If you do good science, practical matters pop up in the landscape."

Lerner believes industry money actually gives the institute more freedom to set its research priorities than if it had to follow the fads in federal funding: "We have the freedom not to be jobbers. There are a lot of

jobbers in science. I'd say 50% of the scientific community run shoe shops. If open-toed shoes are important, you bring in a machine and repair open-toed shoes. You're a captive of somebody else's decision, either intellectual or political, about what to work on. We try not to be."

Still, Scripps' sponsors do more than quietly wait for results with industrial promise to turn up. Both J&J and PPG maintain small labs in the Molecular Biology Building, staffed by corporate scientists with collegial status at the institute.

Scripps' nonprofit charter doesn't al-

low contract research, so the companies offer grants and arrange collaborations with their own scientists to nudge along basic research that seems to have industrial promise.

A case study in how they do so involves the ongoing research on erythropoietin (EPO), a growth factor that regulates red blood cell production. J&J subsidiary Ortho Biotech already markets a version of EPO. Edward S. Golub, director of the J&J lab, thought a knowledge of the EPO molecule's shape and how it interacts with its receptor might lead to the design of an improved EPO. Golub only had to dangle

the problem in front of Scripps' researchers. Now he's funding postdocs in three labs while his own technicians help prepare starting materials for structural analysis.

One of the postdocs works for Peter Wright. Wright comments: "If J&J came to me and said 'Peter, we'll give you lots of money to study this protein' and I think the protein is boring, there's no way I'm going to do it. But EPO, that's a challenge to my technology to take on a problem of that magnitude. And it's a long way from understanding how and where a molecule works to building a drug."

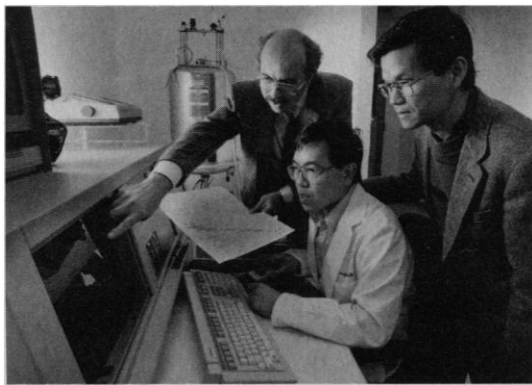
No matter how far off applications may seem, though, both J&J and PPG have the right to review the manuscript when Wright or any other Scripps scientist wants to publish his results. If the industrial sponsors think a result is promising, they can set in motion the disclosure and patenting process before publication. (The companies pick up all filing costs, but the patents remain the property of Scripps.) Officially, the sponsors have 30 days for the review, but they say they take pains not to delay the publishing process. "It's not uncommon to run into someone in the faculty club and have him say, 'By the way, I'm going to give a poster next week,'" says Jonathan Lasch, a chemist who directs the PPG lab. "We discourage that. But our lawyers can do an all-nighter if they have to."

Although Scripps has filed 100 patents in the past decade and signed up more than 100 licensees, royalty income brings in only about \$650,000 a year. Most of it comes from a 1982 patent (still the focus of a long-running court battle with Genentech) on a method of isolating Factor VIII, the blood clotting substance used by hemophiliacs.

Patent income will probably continue to grow. But Lerner says he doesn't aspire to be fully supported by hard money. He values the "edge" that comes from having to survive the peer-review process. He also doesn't want to be as big as his model, Bell Labs. But he's not foreclosing any options.

"We may be just about the right size," Lerner says. Once the current phase of faculty expansion is complete and a new chemistry building is finished, he says, "We'll turn inward and repair those gaps that will occur from retirements. But we're keeping a very watchful eye on science to see where it's going." If he sees a need to move quickly in some new direction, he'll very likely have the resources to do it. ■ YVONNE BASKIN

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**Recent recruits.** Chemists Nicolaou (left) and Chi-Huey Wong flank NMR expert Dee Huang.

at Scripps who are no longer the recipients of this kind of spending. And the lavish startup funds also draw envy aplenty from outsiders. Scripps researchers one after another relate tales of hostile comments from reviewers or from peers, especially ones who don't realize that Scripps researchers, too, have to vie for grants. Ernest Beutler, chairman of molecular and experimental medicine at Scripps, relates a recent lunch conversation with an NIH official: "I complained that we have trouble because people think we have a lot of money. He said, 'Don't you?' It's hard to tell what this may mean in a study