INSTITUTIONAL PROFILE

The Whitehead Institute Reaches Toward Adulthood

Sometimes, it seems, there can be troubles even in Paradise. Of course, no earthly scientific research establishment could live up to an analogy with Paradise, but some are closer than others, and as it approaches its second decade, Massachusetts Institute of Technology's (MIT) Whitehead Institute could, in many ways, make a claim for being among the closest. From the day the private molecular biology research institute burst on the scene in 1982, this godchild of MIT has led what new director Gerald Fink calls a "charmed existence." For one thing, the Whitehead was never an infant but sprang forth a precocious teenager, complete with a remarkably generous allowance from its benefactor, Edwin C. "Jack" Whitehead. Whitehead had made a fortune from Technicon, a company that produced and marketed bioanalytical instruments. He turned over a spectacular $135 million of that fortune as an endowment for the Whitehead—a sum surpassing the endowments of most U.S. colleges. As a result, the Whitehead hit the ground running, with its own administration and a young, energetic, accomplished faculty.

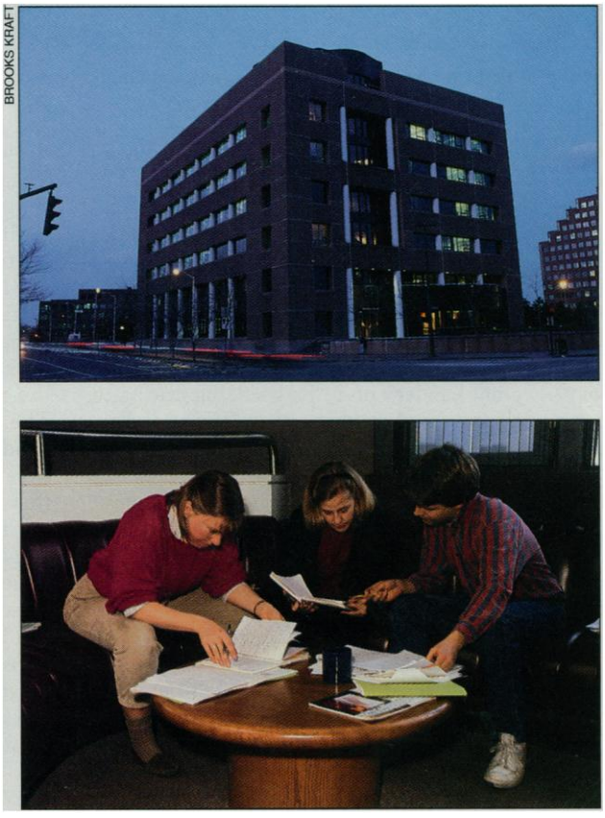
And what a return the institute got on its investment! A very short list of the institute's major scientific contributions would include the discovery of the tumor-suppressor retinoblastoma gene in Robert Weinberg's lab; the discovery of the RAG genes, which are involved in antibody assembly, in the laboratory of the institute's first director, Nobelist David Baltimore; and the discovery of retrotransposition, the process by which yeasts duplicate genes and insert the copies into their chromosomes, in current director Fink's lab. All this—and much more—in less than 8 years from the day the doors opened.

Challenges of success

Indeed, aside from a congressional probe into research done in collaboration with—but outside—the Baltimore lab and Jack Whitehead's sudden death last month, the institute has experienced few misfortunes. But as the Whitehead enters its second decade, it will confront problems posed by that very success. Because the institute provides such an attractive atmosphere for research, few faculty have left, and the institute finds itself graying, with little room to bring in the younger scientists who have been its stock in trade. To Baltimore, this means that to keep fresh ideas flowing, the institute may have to look to the "overall MIT community to provide the youth." But that would be to reopen some old wounds.

Some MIT biology faculty, like Sheldon Penman, best known for his work on the cell's architecture, still resent the Whitehead for having, as Penman puts it, "parasitized the [MIT biology] department" when the institute was formed. Penman is one of the most outspoken members of a vocal minority among the MIT faculty who opposed the institute's creation. Ten years later, this remains a challenge for the Whitehead director. If Penman is right, the MIT biology department doesn't have the young faculty the Whitehead staffers are looking to form collaborations with. Hence Whitehead director Fink may have his work cut out for him.

That work will be a continuation of the work Baltimore did with Jack Whitehead before leaving the Whitehead to become president of Rockefeller University in 1990.



BROOKS KRAFT

Spirit of place. The Whitehead's building in Cambridge includes areas specifically designed to encourage informal interactions among researchers.

Whitehead wanted an independent research institute devoted to biology within an established university, because, he reasoned, it would be easier to attract top faculty and students in that setting. Whitehead struggled to sell this notion to universities around the country for at least 10 years without success. But in David Baltimore he found a partner capable of helping translate the dream into a reality. What Baltimore gave Whitehead was the clout of a Nobel Prize–winner and the expertise of a biology professor at MIT's Cancer Center.

"Unabashed focus" on molecules

That clout was instrumental in overcoming the resistance among some faculty, who were concerned that the university could lose control over the intruder in its midst: a research institute bearing the MIT imprimatur that was essentially independent of MIT (see box on page 27). With Baltimore at the helm, the Whitehead got the go-ahead from the MIT corporation in December 1981, and Baltimore set out to establish the Whitehead's scientific agenda. The outlines of that agenda stemmed from the young visionary's perception (he was then only 43) that remarkable advances were about to come from using the tools of molecular biology to study development and differentiation. "Rather than getting classical embryologists, we had an unabashed focus on molecular biologists and biochemists," Baltimore recalls.

To get that scientific program under way, Baltimore recruited five researchers to form the core of the new institute: from MIT came Robert Weinberg, a specialist in molecular oncogenesis, Harvey Lodish, a cell biologist, and Richard Mulligan, an expert in gene transfer and gene therapy techniques. Fink, a yeast geneticist, was recruited from Cornell, and developmental biologist Rudolf Jaenisch arrived all the way from the University of Hamburg in Germany.

These five provided much of the Whitehead's early character—even working with architects to design the building. And if ever a building served as a metaphor for the personality of the community it houses, it is the Whitehead's facility, located in Cambridge Center near Kendall Square. The building, says Baltimore, "reflects scientists' view of science rather than an architect's view. We wanted to maximize the opportunities for interaction."

To realize that goal, labs were arrayed along two long corridors on either side of the building, with one researcher's lab contiguous with the next to facilitate the flow of people and ideas. Moreover, Baltimore's team and their anointed architects placed areas reserved for socializing at judicious junctures between the

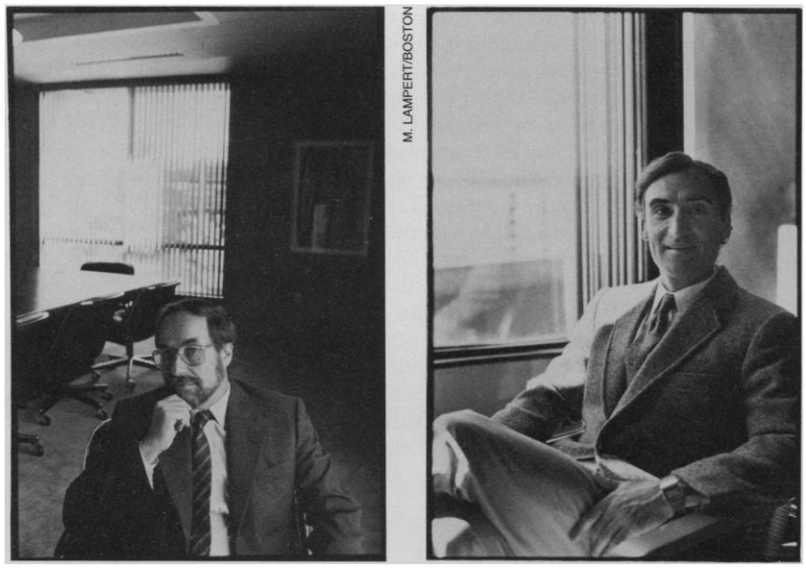
labs. And in case that wasn't enough to create close and casual encounters, there were institute-wide retreats. "This may come as a surprise to some people," says Richard Young, who's been at the Whitehead since 1984, following a postdoc at Stanford, "but Baltimore set up such a highly interactive environment for scientific discussion that he created a collegial atmosphere second to none. It's difficult to spend more than a few days here without making a fruitful collaboration."

The second hallmark of Whitehead success has been youth. Almost from the beginning, Baltimore initiated a program unique to research institutions of the day. He brought in talented young scientists, mostly fresh out of graduate school, and gave them the opportunity to run their own labs as Whitehead fellows. Fellows stay at the institute for 3 to 5 years. Like faculty members, they are expected to obtain grant support, but they are provided with lab space, technicians, postdocs, and generous start-up funds from the Whitehead's endowment. Bruce Tidor, a Whitehead fellow who is developing computer simulations of protein structure, says the position offers big advantages over conventional postdocs: "I've heard from junior faculty that a postdoc did not train them to write grants, run a lab—the administration versus the execution of research. This does both, and that's unique."

Although the Whitehead fellowship wasn't specifically designed to produce full-fledged Whitehead faculty, in a few cases outstanding fellows have been added as members of the institute. Peter Kim, for example, came to the Whitehead as a fellow in 1985 after completing his Ph.D. in structural biochemistry at Stanford. When the young researcher joined the Whitehead, he embarked on a novel study of protein structure, using antibodies instead of the more traditional crystallographic methods. After 3 years, Kim's approach, though promising, had produced no hard results. Nonetheless, his creativity so captivated his Whitehead colleagues that they overlooked his publishing record and offered him a junior faculty position. "Peter Kim was absolutely brilliant. He could design ways of probing protein structure that were unparalleled. It didn't matter that he hadn't published anything," says Baltimore.

Star quality

Another stellar talent who went from Whitehead fellow to Whitehead faculty was Eric Lander. When Lander started his fellowship in 1986, he had an outstanding academic record—valedictorian of his class at Princeton and a Rhodes scholar—but no formal training in biology, having been trained as a theoretical mathematician. Lander had already held a faculty position at the Harvard Business School when a chance meeting with David Botstein, then on the MIT biology faculty, sparked his interest in applying mathematics to genetic mapping. Lander got into his new field slowly, retaining his Harvard appointment while pursuing his Whitehead fellowship. After 3 years, he, too, was offered a tenure-track faculty position.



Whitehead leaders old and new. David Baltimore (left) and Gerald Fink.

"Eric was a self-taught biologist and geneticist. He had published a little bit, but not much, by the time we offered him a tenured position [at the Whitehead]," recalls Baltimore. Baltimore notes that the MIT biology faculty, who must approve all Whitehead faculty appointees, needed some convincing to grant Lander a post. "I argued that Eric had a slant on biology that was unique and effective and that he would be one of our most illustrious professors. And that has happened in a short time." Today Lander is director of the Center for Genome Research, which is part of the international effort to construct a map of the entire genetic material of the mouse, to be compared with the human map when that is completed. Lander is also pleased with the arrangement. "I have been offered more space and more money elsewhere," he says. "But I'm still here."

The scientific success of the Whitehead, and its recruitment of talents such as Kim and Lander, are sparkling achievements. But even the most brilliant adolescent goes through troubled times, and the Whitehead is no exception. The darkest period was triggered by the 1986 publication in *Cell* of a paper on which Baltimore was the senior author. Allegations that collaborator and coauthor Thereza Imanishi-Kari of Tufts University had falsified data started cropping up. Soon the paper was the subject of an internal university review and later of a congressional inquiry.

How to stay fresh?

While no one accused Baltimore himself of fraud, many in the academic community started to question his judgment in defending and possibly covering up for Imanishi-Kari. Many, that is, except at the Whitehead, where the entire institute bore the stress along with Baltimore. "You'd pick up *Science* or *Nature* and say, 'Oh no, not again.' Every time you saw Whitehead Institute, it was a negative thing," recalls Fink.

The negative press has probably ended now that the paper in *Cell* has been retracted and Baltimore has resigned as Rockefeller president. But that doesn't mean Fink's problems as the Whitehead's director have also disappeared. Foremost among those is how to keep the institute fresh and energetic when it has run up against institutional limits. "We're bumping up against the four walls of this building," says Weinberg. To stop the bumping, Fink hopes to expand the physical plant to include larger animal care facilities and a greenhouse to accommodate the transgenic plants that are currently housed in what used to be a storage room.

But one thing that will not change, cautions Susan Whitehead, Jack Whitehead's daughter and an institute board member, is the number of members the institute has: The faculty probably won't grow much beyond its current population of 14. "People were so clear," she says, "without exception, that they want to maintain the size of the institution." And that puts the Whitehead in a bind, because by choosing to keep to its present size, it runs the risk of shutting out creative young talents. Fink says his answer will be found in one of Baltimore's innovations. "My emphasis will be on the fellows program," says Fink. Still, the Whitehead will no longer have the option of retaining outstanding fellows, as it did Kim and Lander, which may give it the reputation of a nice place to pass through on your way to your career.

One way to grow would be to foster new collaborations with the MIT biology depart-

ment. And in Fink's opinion, that's a real option, because the relationship between the two is excellent. "The American marriage should be in as good shape," he says. As in many marriages, however, the partners disagree on how good the relationship really is. While most members of the Whitehead and many biology faculty are in post-honeymoon bliss, others at MIT harbor smoldering resentments. Physics professor Anthony French opposed the creation of the Whitehead 10 years ago and says he would oppose its establishment today. And he is resentful that MIT has been asked to share the blame for some mishaps that are connected to the Whitehead. "It has been my impression that when the press talks about the Baltimore affair, he is identified as an MIT professor, but when there is a scientific success, the Whitehead gets the credit," he says.

Within the biology department itself, the concerns are more pointed. "One fear was that the department would become a second-class group of people, and that has happened," says biology professor Penman. "The department has been bled white by such things as the Cancer Center [a subdivision of the biology department devoted to cancer research, which is housed in its own building] and the Whitehead. [The Whitehead gives] nothing to the parent institution. They steal all the students and teach a few courses. That's crazy. That's not philanthropy," Penman says. And if the Whitehead hopes to find young people among the MIT faculty, says Penman, there aren't any. "People do not come because we've been badly treated. There are no young people to replace what had been a stellar faculty," he says.

That situation could put the Whitehead in a real bind, if not now, then in a few years, as its small, elite faculty begins to age intellectually. Will the Whitehead be able to renew its vigor by finding and hiring tomorrow's Peter Kims and Eric Landers? If it can't, will it age gracefully, or will it simply become one of yesterday's hot places to work? Those are the questions that will certainly make up part of the agenda of Gerald Fink's tenure. But for the moment, while the institute's founding fathers are aware of the problems that accompany aging, they prefer those to the other possibilities. Says Baltimore: "There is a liability to age, but the alternative is even worse."

–Michelle Hoffman

The Whitehead: A Model to Avoid?

To most of the scientific world, the Whitehead Institute is synonymous with excellence in molecular biology. But to those with long memories, the Whitehead is also well known for its beginnings as an independent research institute embedded in a university. That concept sparked an academic civil war when it was introduced to the MIT community, dividing the biology faculty and causing soul-searching among nonbiology faculty as well. And while most of those on both sides of the debate are willing to forget the whole thing, some in the outside world still remember—including the managers of one recently founded private research institute, which has chosen not to follow the Whitehead model.

Edwin C. Whitehead

The institute's story began when Edwin C. "Jack" Whitehead found himself a very rich man with a few "tax problems," according to David Baltimore, the Whitehead Institute's first director. Whitehead's corporation, Technicon, which produces and markets bioanalytical instruments, was doing extremely well, and philanthropy was one way to cut his tax bill and do something useful with his money. So Whitehead approached a number of major universities in the hope of setting up an independent research institute. By the time Whitehead found David Baltimore at MIT, efforts to establish ties with Harvard, Stanford, the Rockefeller University, and Duke had failed.

Baltimore recalls that the institute's founding grew out of a "year-long discussion with MIT," but other faculty members see things differently. According to MIT physics professor Anthony French, the Whitehead's creation seemed almost a fait accompli by the time the faculty heard about it in a July 1981 letter from former provost Francis Low. "The impression many of us had was that the agreement was close," says French.

Many on the MIT faculty felt compelled to speak out. Some were concerned about Whitehead's motives—specifically the profit motive. By 1980, Whitehead had sold his company to Revlon and no longer had the same tax incentive, but some feared Whitehead might demand a share of any royalties from Whitehead faculty patents—or even dictate lines of research to increase his potential patent royalties.

Most of the faculty, however, weren't so concerned about Jack Whitehead's motives as they were about MIT's academic integrity. How, they asked, could MIT maintain control over an institution that was administratively and financially separate from the university? Engineering professor Ascher Shapiro summed up these concerns in an open letter saying, "MIT should not lend its name and reputation to an organization that acts independently of the MIT corporation, administration, and faculty."

In response, the agreement setting up the institute was amended. One key amendment had to do with how the institute selects its staff. Says Low: "They have joint search committees for Whitehead faculty with the MIT biology department." While Whitehead faculty salaries are paid by the Whitehead, appointments are offered jointly by MIT and the Whitehead. And slots were created on the Whitehead board for MIT representatives.

After the amendments, the creation of the institute was put to an all-faculty vote at the university—and 80% voted yes. Some of the critics, however, Sheldon Penman and French among them, are not convinced the vote reflects the faculty's true sentiments. "There's no doubt in my mind that the administration was determined to put this thing through," says French. Penman adds that one administration tactic was to ensure that the balloting was not done in secret—so that opposition faculty would be intimidated into accepting the agreement. Intimidation or no, the faculty did vote to approve in November 1981, and a month later the Whitehead Institute got its approval from the MIT corporation.

Since then, a variety of private research institutes have cropped up, and while they may envy the Whitehead's penchant for scientific success, they don't envy the controversy engendered by being born within the confines of an established institution. In fact, at least one of them has gone out of its way to avoid that kind of flap. The Picower Institute on Long Island, New York, was set up in 1991 with private funds for the purpose of freeing physicians from clinical duties to give them time to do medically related research. Picower president Anthony Cerami says the Picower chose to avoid what happened to the Whitehead. Says Cerami: "We had a similar response [to that triggered by the Whitehead] from medical schools and other academic institutions. I didn't want to spend my whole life setting up an affiliation. We learned from what happened at the Whitehead."

–M.H.