INTERNATIONAL COMPETITIVENESS

In Biotechnology, Japanese Yen for American Expertise

When a gleaming new $16.5 million research center opened on the University of California (UC), Irvine, campus 2 years ago, university administrators saw it as a symbol of the bright future for biotech research on campus. But to others, the modernistic glass and tile building was an ill omen. The reason: While the first floor is home to UC biochemists, doing the kind of basic research on yeast molecular genetics that is the key to the United States' current leadership in biotechnology, the second and third floors are populated by scientists employed by Hitachi Chemical Research Center Inc., which paid for the center's construction. Says Susan Clymer, managing director of NichiBei Bio, Inc. in San Francisco, which advises biotech firms on working with the Japanese, "It gives them a bird's eye view of what's going on in research on campus."

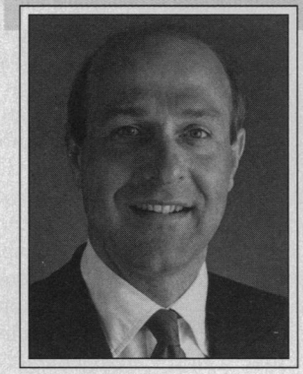
And that's precisely what bothers the UC Irvine center's critics. Even though foreigners have been investing in research in American universities and biotech firms for years, the location of Hitachi right on campus fanned fears that the fruits of research supported by the U.S. taxpayer are being harvested by Japanese investors. The ABC News program "20/20" targeted the center for harsh criticism, while the Center for Public Integrity, a Washington, D.C., think tank, cited the institute as evidence that American universities were "selling out" and that the American mind was being "bought." A recent National Research Council (NRC) report* also cited the case as one of three dozen examples that show "a prevailing pattern of transfer of biotechnology developed in the United States to Japan during the past two decades."

Although Hitachi's research center may be the symbol that strikes fear in many Americans who are worried that the United States will lose its lead in biotech to Japan, it is by no means the most disconcerting example of foreign investment in American biotech. Indeed, some of the fears about the center are based on a misapprehension about Irvine's deal with Hitachi. Like many universities in these arrangements, UC Irvine still owns the patent rights for any product that might come out of the research done on the campus—even if that research is funded by Hitachi. More disturbing, say biotech industry observers, are cases in which Japanese companies tap into U.S. research by buying up U.S. biotech firms. Still worse are cases in which researchers accept Japanese funding in return for the patent or licensing rights to their inventions—yet still accept public funds for their research.

This situation is especially galling to American biotech executives because they say they don't have the same kind of access to basic research, biotech product markets, or patents in Japan. They worry that they will suffer the same fate as the electronics industry, which sold some of its best ideas to the Japanese in the late 1970s—and lost the lion's share of the market to their Japanese competitors as a result. "We heard from a lot of biotech executives here that it's a very uneven playing field," says James Wyngarden, foreign secretary of the National Academy of Sciences and participant in the NRC report.

"The American taxpayer pays for all that research. To allow a foreign country to cherry pick is not a good thing."

–Hubert Schoemaker



Whether that's from Americans' lack of trying or from the Japanese setting up intentional barriers to foreigners' access to research, patents, and drug approval in Japan, everyone agrees that the flow of technology is moving to Japan, rather than from it. "It's not reciprocal," says Ernst & Young partner Steven Burrill, who was a co-author of the NRC report. If nothing's done, the report concludes, the U.S. certainly could lose its strong lead in biotechnology to Japan.

But while that report documents the fact that the biotech executives' concerns are justified, not every link between a Japanese company and U.S. biotech researchers leads to a hemorrhage of ideas toward Japan. Some biotech companies have managed to craft agreements that give them much-needed capital and manufacturing expertise and access to the profitable Japanese drug market—while shielding the ideas percolating in their laboratories. In "a few unusual instances," says the NRC report, there is "clear evidence of a two-way flow." A much-cited example is the 8-year-old joint venture between Amgen Inc. of Thousand Oaks, California, and Kirin Brewery Co. of Tokyo. Back in 1983, the 3-year-old Amgen was one of many biotech firms that had gone public and the company was having a tough time raising the funds it needed for its research program. Recalls Amgen senior vice president Lowell Sears: "We talked to just about everybody that moved."

Kirin, which had just gone into the pharmaceutical business, not only moved, it jumped at the chance to get a piece of Amgen. Amgen researcher Fu-Kuen Li had recently cloned the gene for erythropoietin (EPO), a protein that stimulates the production of red blood cells. That opened the door to producing large amounts of EPO, which can be used to treat patients who are anemic because of kidney failure or treatment for AIDS. Kirin researchers had been trying to purify the EPO protein—but with less success—so it seemed like an ideal match. By early 1984, the two companies had worked out the terms: Kirin put up $12 million and Amgen invested $4 million and contributed the fundamental technology for making EPO. They split the costs of developing and marketing the drug in Japan. Today, and Amgen Kirin share the profits from EPO and another drug, and Amgen has become the sales leader among biotechnology companies with sales of $361 million in fiscal year 1991.

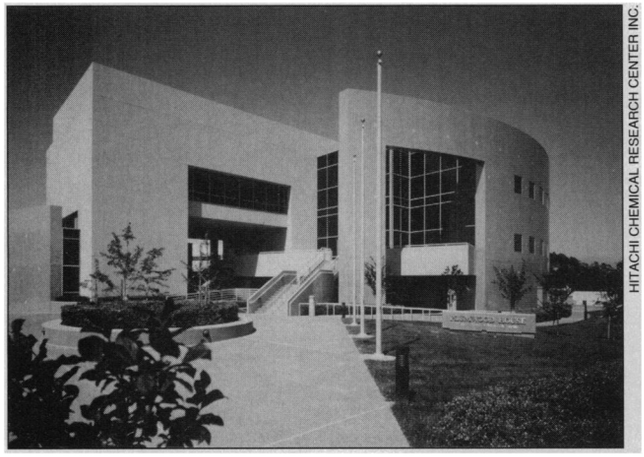
Patient patron. What made this joint venture work so well? "Of all our corporate partners, Kirin has been the most flexible and the most understanding," says Sears. For example, Kirin took a patient, long-range view of its investment—it didn't waver even when it cost $80 million to take EPO through U.S. Food and Drug Administration approval at a time when the joint venture brought in no income. Adds Sears: "If it had been an American company, it wouldn't have worked, because most American companies lack the patience and flexibility." Yet that success didn't require Amgen to endanger its future prospects. "We've never exchanged what I would call discovery research technology," Sears maintains. "We're careful to guarantee the core ability of the company to generate future products."

That was possible partly because Kirin's main intent was not to harvest valuable research but rather to use the joint venture to learn how Americans translate research into biotech products. Kirin now hopes to apply

*"U.S.-Japan Technology Linkages in Biotechnology," National Academy Press, Washington, D.C. 1992.

what it learned from Amgen to develop new drugs from the fermentation products it has created over the years in brewing beer. It also hoped to learn something about the American style of research, says Koichiro Aramaki, vice president of the pharmaceuticals division of Kirin in Tokyo. "The U.S. type of thinking is very different (from that in Japan). Japanese ideas are very similar to each other. Academic science in the United States is more advanced and energetic," he says.

No matter what the goal of a potential Japanese partner, however, a U.S. company



HITACHI CHEMICAL RESEARCH CENTER INC.

Bird's eye view. Hitachi research center at UC Irvine.

can help ensure that the flow of technology moves in two directions instead of one by resisting the temptation to sell off licensing rights to critical research or technology that is important to its future, says biochemist Hubert Schoemaker, cochair of the NRC group and chairman of the board of directors of Centocor Inc., another biotech firm that signed a successful marketing and sales licensing agreement with a Japanese firm. In this era of global companies, it doesn't matter so much whether your partner is Japanese, European, or American. What matters is "who has the marbles," says David Schetter, director of UC Irvine's Office of University/Industry Research & Technology. But not every startup company worried about survival manages to retain the "marbles," and Wyngarden, for one, is particularly critical of those that sell off "extremely valuable technology." An example is Gen-Probe, a San Diego biotech firm that primarily makes genetic probes for diagnosing sexually transmitted diseases. What started as a research and development agreement with Chugai Pharmaceutical in 1988 turned into Chugai's decision to buy 100% of the company for $110 million in 1989.

While Chugai runs the 8-year-old Gen-Probe as a separate, autonomous company, it owns the rights to all of Gen-Probe's research and technology. So far, however, "there has been no transfer of technology to Japan," says Thomas Bologna, president and CEO of Gen-Probe since 1987. "All the profits stay here. We're plowing them into jobs and research here." Other biotech executives point out, however, that there is little to stop the notoriously aggressive Chugai from taking the technology from Gen-Probe home to Japan.

Academic access. Still, what concerns biotech executives and policy makers far more is the recent push by the Japanese to increase their investment in cutting-edge research on university campuses and in nonprofit research institutes. In this type of research, the United States still has the edge internationally, and once that lead is lost, they worry that American consumers will end up buying biotech products made in Japan based on American research. And they get particularly upset when those researchers also receive funds from the National Institutes of Health (NIH) or other government sources. Says Schoemaker: "The American taxpayer pays for all of that research in this country. To allow a foreign country to cherry pick is not a good thing."

One such agreement that raises concerns is the arrangement between Otsuka Pharmaceutical Co. and Sen-itiroh Hakomori, a professor of pathobiology and microbiology at the University of Washington who is well known for his research with membrane glycolipids. He also is the scientific director of the Biomembrane Institute, a non-profit research center affiliated with the university, which was established in 1987 with $5 million in funding from Otsuka. In return for the first right to license any promising developments in the institute, the company also provides about $4 million a year to fund the institute's faculty of 10 Ph.D.s and M.D.s., with the understanding that those faculty members would also find supplementary funding from outside sources.

While most have not, Hakomori does receive about $600,000 a year in a long-term grant from NIH for his research, which led to the discovery of many new types of glycolipids, some of which modify transmembrane signaling and have potential as tumor suppressors. While he conducts the NIH-funded research at his lab in the Biomembrane Institute, he insists that he can keep the results separate from those of the other work he is doing, which can be licensed by Otsuka. And so far at least, Hakomori says, Otsuka has actually encouraged institute researchers to explore alternative arrangements. He points out, for example, that the company recently waived its right to license several ideas coming out of research at the institute, in favor of encouraging the researchers to set up collaborations with interested U.S. firms. "I feel that is a generous arrangement," says Hakomori. Like many academics who accept funds from the Japanese, Hakomori feels that "large Japanese companies are in general less aggressive and concerned with their own bottom line in this type of funding relationship than U.S. or European companies."

Others, however, say that researchers should not be fooled by the Japanese companies' willingness to forgo short-term profits for a long-term gain. Another arrangement that concerns some is a second Kirin undertaking, the nonprofit La Jolla Institute for Allergy and Immunology, established in 1989 just down the street from the University of California, San Diego, the Salk Institute, and the Scripps Research Institute. In this rich biomedical research environment, the new institute employs 40 to 50 Japanese and American scientists, including Kimishige Ishizaka, a former Johns Hopkins University immunologist known for his 1966 discovery of immunoglobulin-E antibodies. The institute received four grants worth a total of $617,847 from NIH this year—and Kirin has first right to patent the work.

The main intent of the institute, says principal investigator Toshiaki Kawakami, is that it provide a "good stimulus" for researchers at Kirin in Japan. But the possibility that work supported by U.S. funding agencies will lead to patents worries some observers. "That's a sensitive issue, because, in a sense, taxpayers are subsidizing a foreign company," says University of Maryland molecular biologist Robert Yuan, who was also a member of the panel that wrote the NRC report. Clymer takes it a step further: "I think it's alarming. We could be empowering the competitor."

What can be done to overcome the one-sided nature of these exchanges between U.S. and Japanese researchers? Few people want protectionist legislation, but Wyngarden predicts that if the Japanese are not careful, Congress will move in that direction. Predictably, most biotech industry executives don't want the government to step in—except to offer tax incentives to encourage biotech firms to form alliances with other American firms and to make the domestic climate better for biotechnology. Or the government could try to pressure Japan to be more friendly to U.S. products. "What we need most is openness and access to Japanese markets and patents," says Gilbert Omenn,

dean of the University of Washington's school of public health.

Clymer has another approach: She suggests that instead of blaming the Japanese for tapping into their research, Americans should learn from their example. "If I were a CEO of a biotech company that had just been targeted for extinction by the Japanese, I'd go to Japan and set up a research center. I'd scour the country for appropriate technology and excellent science." Perhaps the biotech trade organizations should set up offices in Tokyo where they track hot ideas in biotech research and development. She says that the Japanese have been responding to American criticism by opening up more of their research to Americans—but few Americans have been takers so far. What's dangerous, she says, is the "hubris of the United States that they don't have as much to contribute as we do."

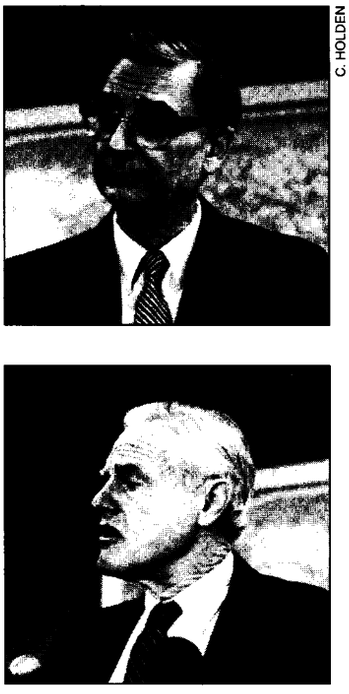
For the near future, however, it is clear that these complex issues will continue to be tested first on American soil. And when East meets West, it may not be a bad idea for both sides to take precautions before they enter into an agreement. There are all kinds of safeguards both sides can take, and UC Irvine and Hitachi covered the waterfront: Before they broke ground on the new research center, not only did they complete a 40-page set of guidelines spelling out everything from sharing Hitachi's DNA sequencers and conference rooms to hiring graduate students, they also asked four Shinto priests to bless the site of the new research center.

–Ann Gibbons

ENVIRONMENT

Scientists' Campaign to Save Earth

The Union of Concerned Scientists (UCS), departing from its traditional preoccupation with nuclear war, is now spearheading a campaign to alert the world to a different kind of holocaust: humans' destruction of their life support system. Last week, it issued a "Warning to Humanity," signed by 1500 scientists from around the world, saying that "human beings and the natural world are on a collision course," which "may so alter the living world that it will be unable to sustain life in the manner that we know."



C. HOLDEN

Sounding the alarm. Edward O. Wilson *(top)* and Henry Kendall.

At a 17 November press conference in Washington, D.C., MIT physicist and UCS chairman Henry Kendall was joined by Harvard biologist E.O. Wilson, Cambridge University astrophysicist Sir Martin Rees, Yale economist James Tobin, and soil biologist Johanna Dobereiner of the Brazilian Academy of Sciences. Characterizing the "warning" as the kickoff to a sustained campaign aimed at government, industry, and religious leaders worldwide, the scientists explained that the plea consists of five basic goals: a curb on environmentally damaging activities such as fossil fuel use; more efficient use of natural resources; stabilization of population growth; reduction of poverty; and equality between the sexes.

Kendall claimed that "an astonishing number of the most senior scientists in the world" have signed the plea—including 99 Nobel Prize–winners, a dozen national academies of science, the Pontifical Academy of Sciences, and the director-general of UNESCO. Conspicuously absent from the roster was Frank Press, president of the U.S. National Academy of Sciences (NAS). An academy spokesman says Press consulted with the NAS council on the matter and decided to reaffirm a "long-standing policy" that it is "unwise" for the NAS president to sign any petition that the academy has not had a role in drafting.

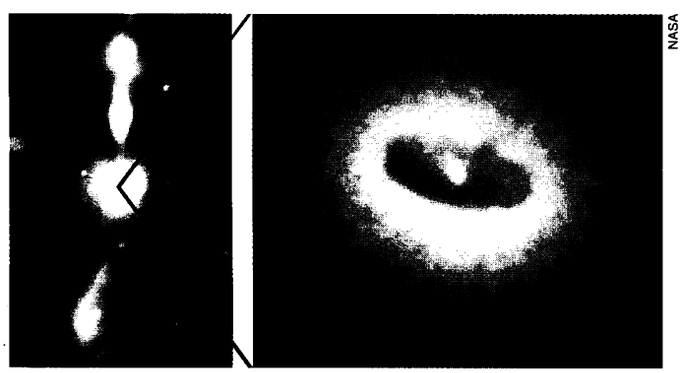
–Constance Holden

ASTRONOMY

Breakfast of a Champion?

Astronomers have long suspected that a massive black hole lies in the center of the galaxy NGC4261. Now they believe they have captured an image, if not of the black hole itself, at least of its breakfast—a 300-light-year wide pancake of dust and gas that appears to be swirling inward toward the putative black hole. This "accretion disk," photographed by the Hubble Space Telescope, could be the energy source for the black hole—if it exists.

Researchers focused Hubble on NGC4261 because, like some other galaxies, it shoots out two "jets" of energetic particles that act as powerful beacons of radio waves. To some astronomers, such jets are like the spout of a whale—a sign that a black hole containing millions of times the mass of the sun lurks at their base. The energy powering the jets, theorists speculate, is generated as the black hole sucks in material from a surrounding accretion disk. The disk "is the storage place—where material works its way into the hole," says Walter Jaffe of the Leiden Observatory in the Netherlands, who led the group that made the observation.



NASA

Thar she blows. 45,000-light-year-long radio jets (seen in the ground-based image at left) spout from a disk and possible black hole.

And now Jaffe and his colleagues have spotted a picture-perfect disk ringing the base of the jets—the first convincing evidence of an accretion disk ever seen, he says. "The idea of these disks has been around for a long time, but now we are finally seeing one." And in just the right position, perpendicular to the jets, notes astronomer Daniel Weedman of Pennsylvania State University. "That alignment to me is the most important thing," he says. But he notes that even though the other pieces of the picture are in place, the evidence for the black hole itself is still circumstantial. "I have reservations," he says. "I don't think we truly know what's going on in that spot in the center of the disk."

Jaffe agrees that astronomers have yet to prove the existence of any black hole. But he expects to have a strong case for this one as soon as he can measure the speed of material swirling near the center of the disk, to see if the mass dragging it inward is more than 10 times that of the sun. No other object could pack the necessary mass into such a small space. "Then it will be hard to say it's not a black hole," Jaffe says.

–Faye Flam