

## SCIENCE AND BUSINESS

# Cuba's Billion-Dollar Biotech Gamble

### 1. Jocelyn Kaiser

*Fidel Castro has staked the lion's share of his country's science resources on biomedicine; surprisingly, Cuba's foray into this high-risk capitalistic arena appears to be paying off*

**HAVANA, CUBA**—On a balmy fall afternoon in this city of crumbling Spanish piazzas, a power outage has sent office workers out the door early, to climb on bicycles or thumb rides on streets tangled with beaten-up Soviet Ladas and 1950s Chevrolets. Hunkered down inside the Center for Genetic Engineering and Biotechnology (CIGB), however, researchers work with the buzz of a beehive, their incubators and centrifuges humming along thanks to the center's emergency power plant. Many of the 700 researchers at this sprawling complex on Havana's western edge won't get home until late in the evening, wiped out from another long day.

Although Cuba remains an impoverished nation hobbled by ill-conceived central planning and the U.S. economic embargo, the country has begun to attract attention for a surprising reason: its huge investment in biotechnology. President Fidel Castro has poured over \$1 billion in the past 8 years into a palm tree-lined biomedical campus that's like a hybrid of the U.S. National Institutes of Health (NIH) and a generic drug company. He is staking much of his nation's science resources on a roller-coaster industry dominated in the United States, at least, by venture capitalists. The communist leader's improbable devotion to biotech has raised eyebrows among industry and academic experts. "It's a very risky investment for the Cuban government," says Allan Bernstein, a molecular biologist at the Samuel Lunenfeld Research Institute in Toronto, Canada.

But, perhaps equally improbably, this grand capitalistic experiment shows tantalizing hints of succeeding. Several thousand scientists at Havana's biomedical campus and at satellite centers have already developed a couple of dozen products, including monoclonal antibodies, streptokinase—a drug used to break up blood clots—and the world's only available vaccine against meningitis B (see table). Under development are cancer vaccines and other compounds that would be considered cutting-edge in U.S. labs.

"It's a very impressive place, very vital," says NIH director Harold Varmus, who visited CIGB in 1993. "They've got an excellent pool of scientists, the best in Latin America, no question," adds James Larrick, president of the Palo Alto Institute for Molecular Medicine in California. And the clean rooms, fermenters, and purification lines in Cuba's drug factories are top-notch, Larrick says: "some of the best in the world outside of the United States and Britain."

A Sample from Cuba's Biotech Cornucopia

	In trials	On market
Hepatitis B vaccine		×
Meningitis B vaccine		×
Tick vaccine		×
Monoclonal antibodies for kidney transplants		×
Epidermal growth factor for wound healing	×	
Cancer vaccines	×	
AIDS vaccine	×	
Hepatitis C vaccine	×	
Fast-growing tilapia	×	
Pest-resistant sugar cane	×	

But Cuba's fledgling industry faces major obstacles to competing with its rivals in developed countries. The 38-year-long U.S. embargo has isolated researchers from colleagues and pharmacy shelves in the United States (see [sidebar](#)), and Cuban biomedical institutes are only haltingly gaining the acumen needed to market products. Cuban biotech officials admit they have a long way to go to secure a place in the world market. "This is a new industry in Cuba," says CIGB director Manuel Limonta. "In many places in the world, biotechnology companies don't even have revenues."

Cuban scientists don't blink when asked the inevitable question: How does the entrepreneurial spirit that drives biotech elsewhere survive—even flourish—in a communist dictatorship? The answer: They are driven by a desire to help their community, not to make money, they say. "It is the dream of any scientist" to develop a new drug or transgenic crop, says

Cristina Mateo of the Center of Molecular Immunology (CIM). But the bottom line is still a consideration, Limonta says. "We have the idea of doing business the way it is done by any biotechnology company in the world."

## Building a human machine

Behind the biotech boom is Fidel Castro himself, who since seizing power in 1959 has made public health a priority—Cuba's infant mortality rate is the lowest in the developing world. "Fidel is like our principal scientist. He has encouraged and pushed all research in the biotechnology field," says René Robaina of the Center for Immunoassays.

What sparked Castro's interest was a visit to Cuba in 1980 by R. Lee Clark, former president of the M. D. Anderson Cancer Center in Houston, who talked up the wonders of interferon, then seen as a possible cure for cancer. Castro dispatched six scientists to the lab of Finnish virologist Kari Cantell, who had developed a method for making interferon from white blood cells. Back in Cuba, working in a house converted into a lab, "in less than 2 months we had interferon produced by our own hands," says Limonta, who headed the group. A dengue epidemic hit the country in 1981, and Cuban doctors found that the homegrown interferon deterred a complication of the disease, internal bleeding. "The government could see that this kind of work did give some return to society very quickly," says Pedro López-Saura, CIGB's clinical trials director.

And that was just for starters. Limonta's group began making recombinant interferon and churning out antibodies to it. (The drug never panned out as a cancer cure-all, but it has found use against other diseases.) Despite losing a bid for a new United Nations biotech center, Cuba in 1986 invested \$120 million to build CIGB and launched several institutes nearby. The labs began training a cadre of scientists, most of whom won the coveted privilege of working abroad for a year or two.

The fledgling campus was under immense pressure from Castro to catch up with the rest of the world. CIGB staff grew accustomed to mandatory 14-hour days and a top-down agenda; one émigré who left CIGB in 1993 calls the conditions there at the time "slavery." Even today, some young scientists eager to be chained to the bench wind up "frustrated" in quality control, says one U.S. scientist. López-Saura defends the system. "We are a small country and a poor country." Young people, he says, "know they are not coming to science to win a Nobel Prize."

At first the campus focused on products for use in Cuba, cranking out preparations tested elsewhere. But after the Soviet Union collapsed in 1991, depriving the country of billions of dollars a year in subsidies from its patron, Cuba began peddling its wares abroad, especially in Latin America. These products now include everything from a hepatitis B vaccine to immunoassays that require one-tenth as much reagent as standard plates, putting blood tests for neural tube defects, AIDS, and other conditions within reach of dozens of developing countries. Cuba rakes in about \$100 million a year from such products—a drop in the bucket, perhaps, to most any U.S. firm with a drug on the market. Nevertheless, says CIGB immunologist Jorge Gavilondo, the sales prove that "we have grown from a scientific institute to a biotech company."

Like any biotech company, CIGB and other Havana institutes pride themselves on their pipeline. Basic research is a growing part of CIGB's portfolio, says Limonta. CIGB and other institutes are working on vaccines against hepatitis C, dengue, and cholera, among other diseases. CIM, meanwhile, has pioneered cancer vaccines that trigger an autoimmune response to epidermal growth factor receptors, which are overexpressed in certain tumors, and to gangliosides found on tumor cell membranes. Nicholas Restifo of the U.S. National Cancer Institute calls their ideas "really fresh and interesting."

Not everything the Cubans have touched has turned to gold. A much-touted initiative to develop an AIDS vaccine has faced the same stumbling blocks that bedevil similar efforts in other countries. Two years ago, CIGB gave 24 volunteers a cocktail of GP120 HIV coat proteins, which did trigger an immune reaction. The institute plans to carry out further trials next year. But most groups outside Cuba are now combining GP120 with other strategies that prime the body's cell-mediated immune response. "There's more optimism" about this approach "than there is about just using GP120," says Susan Zolla-Pazner, an AIDS researcher at New York University.

Still, observers say, the advances clearly are outpacing the setbacks—an amazing feat considering that the country, aside from its booming tourism industry, endures rationed food and gas, a dearth of basic medicines like aspirin, and minuscule wages. (Scientists at the biotech centers get perks like subsidized meals and rides on company buses, but they earn only about \$20 a month.) And, in spite of its privileged status, the biotech effort finds itself chronically short of funds in the wake of Cuba's economic crash a few years ago. Researchers scrounge for supplies and rely on foreign collaborators for access to pricey techniques such as x-ray crystallography. "They can't just experiment and waste reagents," says Eva Harris, a molecular biologist at the University of California, Berkeley, who collaborates with researchers in Cuba.

Despite these problems, Cuba's biotech researchers enjoy plum conditions compared to scientists in other fields. "The decision obviously has been made to pool resources into this one area to the neglect of other areas," says U.S. National Science Foundation director Rita Colwell, who visited Cuba last year as part of a mission led by the AAAS, which publishes *Science*. "The emphasis is put on biotechnology because this is the most promising and able to bring back economic support to the whole system," explains Ishmael Clark, president of the Cuban Academy of Sciences. Rank-and-file scientists seem to share this outlook. "It's a very strategic area. We don't complain," say University of Havana physicist Ernesto Estévez.

## After the revolution?

For scientists who believe in Cuba's biotech dream and are determined to remain in the country, the elusive goal is breaking into markets in developed nations. But Cuba faces many obstacles, including the high costs of getting approval to sell products in such countries. Cuba is "weak" in quality-control standards and marketing skills and has only recently begun applying for patents, notes Mikael Jondal of the Karolinska Institute in Sweden, who 2 years ago served on a European fact-finding mission to Cuba. Cuban leaders respond that their labs now adhere to international standards for quality control and clinical trials.

A deal that Cuba inked with a Canadian company in 1994 offers reason for optimism but also shows the challenges the country faces. The firm, York Medical Inc., is acting as a partner to get Cuban products through Canada's regulatory hoops and then license them to drug companies. But of the five products it tapped as most promising, one—streptokinase—has lost major ground to another drug, TPA, says CEO David Allan; and a method for selecting the best antibiotic for a patient lost its allure when a U.S. company upgraded its system. Allan's firm is pinning its hopes on four cancer antibody products, now in clinical trials in Canada, as well as a combined antifungal and antibiotic.

The central concern of many observers is how long Cuba can maintain the seeming paradox of engaging in a high-risk, profit-driven industry in a state-controlled economy. "I don't think they're going to be able to do really cutting-edge biotech in a top-down world," Restifo says. "There would be hundreds of small Cuban biotech companies if the country was friendly to entrepreneurial endeavors," adds Larrick.

But Cuban researchers are optimistic. "We will succeed to sell products in the First World," predicts López-Saura. And many remain staunchly loyal to the system that made this biotech gamble. "I owe my career, my son's and daughter's careers, my master's degree, my Ph.D. degree in Sweden to the government," says CIM scientist-turned-marketing executive María Pascual López. Adds her institute's director, Agustín Lage: "These are moral values and sometimes this is difficult to explain."