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

Cuba's Billion-Dollar Biotech Gamble

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.

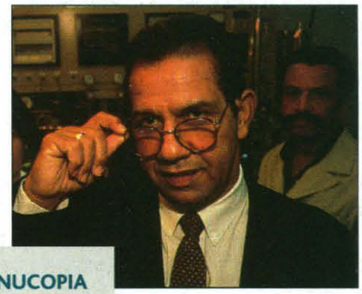
Although Cuba remains an impoverished nation hobbled by ill-conceived central planning and the U.S. economic embargo, the country has begun to attract attention for a surprising reason: its huge investment in biotechnology. President Fidel Castro has poured over $1 billion in the past 8 years into a 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."

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."



Entrepreneur. Manuel Limonta has made Cuba's biotech investment pay dividends, putting products on the market.

PHOTO: DAVID ALAN HARVEY/MAGNUM PHOTOS INC.

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	✔	

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

Embargo Impedes Scientific Headway

They may not always see eye to eye on politics, but scientists in Cuba and in the United States agree that a tightening of the U.S. embargo in 1992 and restrictions on travel between the countries have hindered science—making Cuba's biotech exploits all the more impressive (see main text). Says the University of Havana's Ernesto Estévez, "In science, you feel [the embargo] every day."

The embargo is unusual in that it even bans trade in food and restricts sales of medicines. It was tightened in 1992 by the Cuban Democracy Act, which bars business in Cuba by non–U.S. subsidiaries of U.S. companies. As a result, Cuban scientists buy most of their supplies from Europe. This adds delays and can triple costs, especially for items such as restriction enzymes or spare parts that are made only in the United States and must be purchased from a middleman.

U.S. policy also cramps intellectual growth: Curbs on travel between the countries isolate Cuban scientists from colleagues and conferences in the United States. "It's a blockade of our knowledge," says Pedro López-Saura, clinical trials director at the Center for Genetic Engineering and Biotechnology in Havana. "The United States is the country with the highest scientific development in the world where most meetings take place, where you get the best training." He and his colleagues wishing to attend meetings don't always receive a visa from the U.S. State Department in time, or at all. And U.S. scientists who want to do research or attend meetings in Cuba must apply for a license to spend money there under rules imposed 4 years ago (*Science*, 23 September 1994, p. 1803). "There's tremendous potential, a lot of enthusiasm, and to have them marginalized from the mainstream scientific community is an error and a shame," says National Institutes of Health director Harold Varmus.

The embargo has also impeded at least one initiative to improve public health in the United States, so far blocking attempts by the British drug giant SmithKline Beecham to license Cuba's meningitis B vaccine. Although questions remain about whether the preparation protects young children, it is the only vaccine on the market against group B meningococcal meningitis, a disease that accounts for nearly half the 300,000 cases and 35,000 deaths from meningitis each year worldwide.

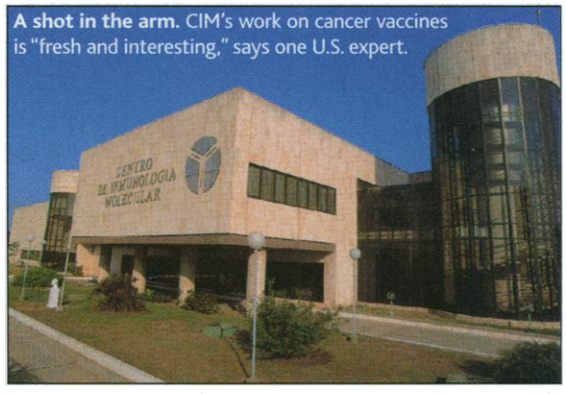
SmithKline wants to work with Cuba's Finlay Institute to improve the formulation at the company's vaccine center in Belgium, but the facility is owned by a U.S. subsidiary. The company has applied for an exemption from the U.S. Treasury Department, pledging to compensate Cuba in part with food and medicine. Fourteen members of Congress, including Republican senators Richard Lugar and John Warner, signed a 6 October letter backing the proposal; SmithKline is hoping for a decision by the end of this year. **–J.K.**

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."



A shot in the arm. CIM's work on cancer vaccines is "fresh and interesting," says one U.S. expert.

CREDIT: CIM

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 Ismael 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." **–JOCELYN KAISER**

CIRCADIAN RHYTHMS

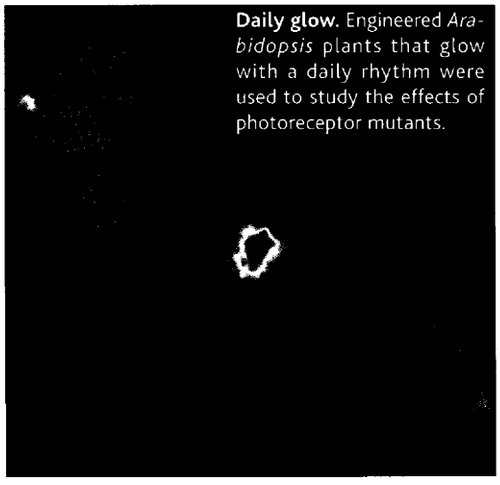
Clock Photoreceptor Shared By Plants and Animals

Cryptochrome, a light-absorbing molecule first discovered in plants, apparently helps light to set the daily clocks of *Arabidopsis*, fruit flies, and mice

You arrive in a new time zone, go to a hotel, and wake up after a long, disorienting sleep. How do you tell if it's day or night? Light is a good cue, and not just for your mind. Deep in your brain, a molecular clock that oscillates with a 24-hour rhythm, pacing your physiology, also relies on light to keep it in synch with the day-night cycle. But even as researchers have discovered many of the components of the clock mechanisms that operate in organisms ranging from bacteria to humans, a major mystery has remained: the identity of the light-capturing molecules that transmit the light signal to the clock. Now, three research teams have fingered a suspect—a light-absorbing protein called cryptochrome that may play that role in organisms ranging from plants to mammals.

Last week, a team led by Steve Kay of The Scripps Research Institute in La Jolla, California, reported in *Science* that cryptochrome is a circadian photoreceptor in plants, while another paper in that same issue from Aziz Sancar's team at University of North Carolina, Chapel Hill, suggested that it might be one in mice as well (*Science*, 20 November, pp. 1488 and 1490). And this week, Jeff Hall and Michael Rosbash of Brandeis University in Waltham, Massachusetts, and their colleagues report in *Cell* that the protein plays a similar role in fruit flies.

The results indicate that cryptochrome is not the only molecule that relays light signals to the circadian clocks in these species. And the data from mice are controversial: Some researchers say that rather than proving cryptochrome is a light sensor, they suggest it could be part of the mouse clock mechanism itself.



Daily glow. Engineered *Arabidopsis* plants that glow with a daily rhythm were used to study the effects of photoreceptor mutants.

CREDIT: ANDREW J. MILLAR

But just finding that cryptochrome plays a role in clocks ranging cross-kingdom from plants to mammals is "an amazing development," says clock researcher Gregory Cahill of the University of Houston, and "the most extreme example of people finding homologies in clock-related genes across species." Besides filling a gap in our knowledge of circadian clocks, the work could also lead to new remedies for jet lag that might mimic or enhance the process by which light resets the clock mechanism.

That mechanism, the biological equivalent of the gears and springs in a watch, is a set of proteins whose levels rise and fall in a daily cycle. The proteins regulate their own oscillations by turning their own genes on and off; light can shift or "entrain" a clock by raising or lowering the level of a key clock protein and so influencing that feedback process. For example, in fruit flies, the clock protein Timeless (TIM) reaches high levels at night and turns its own gene off. Light causes quick destruction of TIM, allowing the *tim* gene to turn on and jump-starting the next daily cycle. To do that, the light must be captured by photoreceptors, which could be either in the same cell as the clock or some distance away, such as in neurons of the eye.

Clock researchers began to suspect that cryptochrome might be such a photoreceptor shortly after Anthony Cashmore and his colleagues at the University of Pennsylvania in Philadelphia discovered it in 1992, in the plant *Arabidopsis thaliana*. Cashmore's team showed that the protein, which is sensitive to blue light, is important for a variety of light-based growth responses in plants, such as bending toward light.

Findings such as those prompted Kay and his postdoc David Somers to test whether cryptochrome transmits light signals to the *Arabidopsis* circadian clock. To