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"Cuba's future must, by necessity, be a future of scientists," Fidel Castro declared in 1960, soon after the Cuban revolution. Almost 40 years later, his prophesy is some way from fulfilment. But in one area of applied science — biotechnology — a concerted national effort instigated by Castro himself has made independent progress unmatched elsewhere in the developing world.

Until the 1960s, Cuba had no state-sponsored science programme. "Before the revolution, there were scientists in Cuba, but no science," says Gustavo Kouri, director general of the Pedro Kouri Institute of Tropical Medicine in Havana. Ismael Clark, president of the Cuban Academy of Sciences (which was founded in 1861, two years before the US National Academy of Sciences) points out, however, that Cuba has a 200-year history of outstanding scientists. The most famous is probably Carlos Finlay, a Cuban physician who in 1881 suggested that yellow fever and similar diseases could be transmitted by mosquitoes. This was the first suggestion of 'vector-borne' disease.

After the revolution, the universities were reformed to teach science, and throughout the 1960s and 1970s thousands of students were sent abroad for advanced scientific training. The first Cuban multidisciplinary research centre, the National Centre for Scientific Research (CNIC), was founded in 1965. In 1981, biotechnology work began with the production of interferon-α (see box).

Daniel Codorniú, vice-minister of science at the Ministry of Science, Technology and the Environment (CITMA), says that Cuba has invested at least US$1 billion in biotechnology over the past 15 years. Of this year's science budget (officially US$125 million), 30 per cent is for biotechnology-related projects. Most of this is applied research directed at developing therapies for Cuba's public health problems.

'Protocol 149 house' where interferon was first made.

Cuban officials claim that the fruits of this research already earn enough in exports to sustain the biotechnology research programme, although they won't provide details. Products are sold under government control and the proceeds usually go to the treasury. Agustin Lage, director of Havana's Centre for Molecular Immunology (CIM), says: "Biotechnology is not yet a major exporter like the sugar cane or tobacco industries, but it could be an important part of the economy in the future."

Export of vaccines

Most of the fledgling industry's income comes from just two products. One is a hepatitis B vaccine, now in the process of certification by the World Health Organization (WHO), which is exported to more than 30 countries. The other is the world's only known vaccine against meningitis B.

In Cuba in the 1980s, 150–200 children were dying of meningitis each year. Vaccination was carried out, but there was no vaccine against serogroup B. The A and C vaccines are based on polysaccharides in the bacterial capsule, but the polysaccharides of meningococcus B do not confer immunity in humans. So Cuba developed a vaccine using outer membrane proteins of B, capsular polysaccharides of C, and a structural protein common to both. The vaccine showed an efficacy of 83 per cent in phase II clinical trials, and by 1990 all infants over three months old were being immunized.

Export sales were not a primary objective at the time of the vaccine's development, according to Orlando Gutiérrez of the Finlay Institute where it was developed. But Cuba began to export the vaccine in 1989, when Brazil had an epidemic of meningitis and sought help. Since then, about a dozen other countries have purchased and licensed it. The vaccine is currently being tested in Britain, and SmithKline Beecham would like to manufacture it in its Belgian vaccines division. Under its embargo policy, the United States is now trying to penalize companies that trade with Cuba, but SmithKline is seeking an exemption from such penalties.

Vaccination is a major focus of the Cuban health system, whose childhood immunization programme has led to the eradication of measles, mumps and polio, as well as a 30-fold decrease in the incidence of meningitis. Vaccine development is therefore a natural priority for Cuban biotechnology. A recombinant subunit vaccine for human immunodeficiency virus (HIV) (directed against the viral protein gp120) is in clinical trials, with a DNA vaccine in development. Also on trial are vaccines against hepatitis C, leptospirosis and cholera. There are projects to develop

How Castro's enthusiasm for biotech

In 1980, when the world was talking about interferon's promise as a potential cure for cancer, Fidel Castro made the decision that Cuba should have it too. He sent six scientists, led by Manuel Limonta, abroad to learn how to produce interferon. A small house in western Havana was outfitted as a laboratory, and the scientists set to work. They worked non-stop, with Castro himself visiting daily to check on their progress. On the forty-second day, the laboratory produced natural interferon-α, and Cuban biotechnology was born.

In 1982, a Centre for Biological Research (CIB) was founded near Havana, and by 1986 Limonta was the director of the Centre of Genetic Engineering and Biotechnology (CIGB), with a staff of 1,080. The CIGB is now one of a cluster of 38 pharmaceutical and biotechnology establishments located on the west side of Havana.

The CIGB has products registered in 34 countries and a total of 128 registrations worldwide. These range from diagnostic systems, vaccines and transgenic plants and animals to products for use in industrial processes. Like most of the units in the cluster, the CIGB undertakes research, development and production under one roof.

Cuba's hepatitis B vaccine was developed here. Recombinant versions of interferon-α2b, interferon-γ, interleukin-2, epidermal growth factor, erythropoeitin and streptokinase are other major exports, as is the world's only effective vaccine against cattle tick. Diagnostic systems for HIV-1 and hepatitis C are exported to Latin America, China and India, and a recombinant product for use in cheese

Che Guevara (right) founded a laboratory in 1964 to research uses of sugar cane derivatives.

vaccines against *Haemophilus influenzae*, salmonella and dengue haemorrhagic fever — the last is a particularly difficult project, as vaccines must be effective against all four dengue viruses to prevent disease.

New products successful

The first scientific institute founded after the revolution was the Cuban Institute for Research on Sugar Cane Derivatives (ICIDCA), established in 1964 by Che Guevara . It was hoped then that these derivatives would some day become more important than the sugar itself, and so it is apposite that one of Cuba's most promising new products — PPG, or policosanol — is an 8-alcohol extract of sugar cane wax.

PPG is a cholesterol-lowering drug that is safe and well tolerated even in elderly patients. Even from the early stages of development, the chemists involved thought that this product looked promising: according to Rosa Más, who directed the project, that's how it got its name. The acronym is taken from 'producto para ganar' (money-making product) — appropriately enough, as PPG is now registered in 26 countries. Most of these are developing countries, because of the competition from cholesterol-lowering drugs from first-world companies, but Castro claims that PPG is used by patients in Miami.

Of the major biotechnology institutes, it is CIM that is doing the most basic research. Its scientists are interested in the immune system, especially its role in cancer and autoimmune disease, and they are working on developing immunotherapy for cancer.

Scientists highly favoured

The scientists in these programmes are favoured by the Cuban state. They receive about double the national average wage, and a number of fringe benefits. At the Finlay Institute, for example, senior staff are either housed on the premises, or provided with transport to and from work. Meals, clothing and child care are provided, and employees receive twice-yearly bonuses in US dollars.

"No system can advance science and technology more than socialism," Castro has declared, "because no other system can look for such integration and cooperation among all scientists, all science research centres, all professionals, all hospitals…." The country's political system certainly allows him to direct research in a way that would be impossible in most other countries. The obvious drawbacks of the system include the fact that most of Cuba's research is very applied and becoming more so. There is little room for curiosity-driven research or individual research pursuits. No one complains about any aspect of the system to outsiders, and it is unclear if they have the freedom to criticize it internally.

It is hard to say whether Cuba's approach to science and technology has been a success. If judged by citation statistics, the results are not particularly impressive. The impact factor of the average Cuban paper is 39 per cent of that of the world average, according to the Institute for Scientific Information (ISI) in Philadelphia, compared with an average of 55 per cent in the rest of Latin America. The impact factor of Cuban papers has doubled over the past 12 years, however, and it is higher in some areas: in pharmacology, for example, the impact factor is a respectable 87 per cent of the global average.

Castro oversaw the establishment of the CIB in person.

But despite a difficult situation, exacerbated by the US embargo, the scientists are clearly doing good work. They have had some commercial success with their products, and have won the respect of those in the international community who collaborate with them. Perhaps most impressively, life scientists have succeeded in addressing several important public health problems with modest resources and little access to the ideas or materials available in the rest of the world.

spurred vaccine development

production is now being licensed in Spain.

Vaccine projects include vaccines for HIV-1 and hepatitis C (both now in trials) as well as human papilloma virus (HPV), dengue haemorrhagic fever, and a recombinant version of the meningitis B vaccine developed by the Finlay Institute.

Plants including sugar cane, papaya, potato, coffee, cabbage and tomato are being genetically modified at the institute for increased resistance to pests and disease, and transgenic sweet potatoes with an improved amino-acid balance are being developed. Development of transgenic sugar cane with a lower lignin content and a higher sugar yield is under way, as sugar cane fibres are used widely for paper and animal feed, and a high lignin content reduces their suitability. Field trials take place following internationally recognized safety guidelines, institute staff claim.

Staff are also working on cloning rabbits and cattle, using the nuclear transfer technique that produced Dolly the sheep. More traditional transgenic approaches have been used to produce mice and rabbits that express human proteins such as tissue plasminogen activator, growth hormone and erythropoeitin in their milk. And transgenic fish have left the laboratory for supermarket shelves: last year 30 tonnes of transgenic tilapia were produced.

There has been no adverse public reaction to these genetically modified foods, although it would be difficult for anyone with doubts to express them in Cuba. Science and biotechnology are, after all, priorities of the revolution. "People trust science; they've seen how it has improved their lives," says Limonta.