Cuba—innovation through synergy

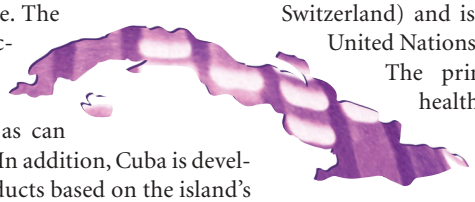
Halla Thorsteinsdóttir, Tirso W Sáenz, Uyen Quach, Abdallah S Daar & Peter A Singer

CUBA'S outstanding achievements in health biotechnology are a source of inspiration for the developing world. They are all the more impressive considering that the island is a small, relatively poor country that has suffered serious economic difficulties for more than a decade. These economic problems arose in the wake of the Soviet Union's disintegration and the political changes in Eastern Europe in the early 1990s, resulting in the collapse of Cuba's export markets, and the imposition since 1961 of a US trade embargo against Cuba, which has limited opportunities for the country's agriculturally based economy. Despite these difficulties, Cuba's strong and continued emphasis on science since shortly after the 1959 revolution has resulted in a highly developed health biotechnology sector.

The success of Cuba's health biotechnology sector

Cuban-based biotechnology has already produced a wide array of products. When 32 Cuban experts interviewed for this study were asked to identify an example of a successful Cuban health biotechnology product, all of them identified the meningitis B vaccine. Developed in the 1980s and based on local research and development, it was the first of its kind in the world, because no vaccine had previously been developed against this strain of meningitis. A more recent example of success is the world's first human vaccine with a synthetic antigen for *Haemophilus influenzae* type b (Hib) (see **Box 1**).

Vaccines have been a particular focus for Cuban biotechnology. Ongoing work includes research on recombinant Dengue vaccine, preventative and therapeutic AIDS vaccines, cholera vaccine and a cancer therapeutic vaccine. The sector has also successfully produced diagnostic tests and therapeutics, as can be seen in **Table 1**. In addition, Cuba is developing natural products based on the island's flora. An example is the natural anticholesterol drug policosanol (PPG), an 8-alcohol extract derived from the wax of one of the country's main crops, sugarcane.



Cuba began development of its health biotechnology sector by imitating products developed elsewhere, such as interferon-α 2b (IFN-α), but in recent years greater emphasis has been placed on innovation from within Cuba. The perception that innovation is increasing is supported by biotechnology experts, such as James Larrick, an entrepreneur in Palo Alto, CA, who says: "Their pipeline is very, very deep now.... It's gone into an adolescence and it's looking pretty good."[1] Indeed, researchers in Cuba have filed about 500 patent applications in the health biotechnology sector based on more than 200 inventions (according to an analysis of the European Patent Office's (Munich, Germany) database, the European Network of Patent Databases, May 2003, http://www.european-patent-office.org/). These have been filed in several countries throughout the world, including the United States, Europe, Brazil, India, China and South Korea. Cuba exports biotechnology products to more than 50 countries, mainly in Latin America, Eastern Europe and Asia. Cuba's hepatitis B vaccine has been certified by the World Health Organization (Geneva, Switzerland) and is prequalified for use by United Nations purchasing agencies.

The primary focus of Cuba's health biotechnology has been on developing products, rather than basic research. As a result, the strength of the country's sector is not truly reflected by its productivity in scientific publications (see **Fig. 1**). Data derived from Science-Metrix (Montréal, PQ, Canada) show Cuban papers to be modestly represented in international peer-reviewed journals, although the number has slowly increased during the past decade[2]. The country's patent activity, on the basis of inventors' addresses of health biotechnology patents granted in the United Status Patent and Trademark Office (USPTO, Washington, DC, USA) carried out in July 2004 (http://www.uspto.gov/), also reflects a modest, but increasing, level of activity. This contrasts with the impressive number of patents at the European Patent Office.

Main features of the Cuban sector

Cuban health biotechnology has reached its relatively advanced stage of development because of the vision of its political leaders and their continued commitment to promote the sector, despite difficult economic conditions, which might have slowed its development to the level it might have otherwise reached. Public research institutions form the backbone of the sector and often

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have commercial branches involved in manufacturing products. The tight integration, advanced development and close government control of the country's health system and biotechnology sector have all promoted the adoption of cost-effective treatment options and encourage collaboration between basic and clinical researchers. In addition, the highly educated population has a positive perception of the sector and readily participates in clinical trials, facilitating the development of new products.

Government. Given that Cuba is a socialist country, it is not surprising that the government has been the main supporter for the development of the health biotechnology sector. Fidel Castro and his government became interested in the potential of biotechnology early in the 1980s when the field of biotechnology was in its infancy. They gave a strategic importance to modern biology and biotechnology, setting up various institutions and creating an interdisciplinary group, the Biological Front, to explore possibilities for Cuba. The Front was a forum to integrate inputs from a variety of scientists in Cuba and was linked to the highest political organization, the Council of State. This marked one of the first attempts to integrate actors systematically and increase their linkages to promote the development of the health biotechnology sector in Cuba.

During the 1990s, Cuba experienced serious economic difficulties, the so-called Special Period, caused by the collapse of its major markets in Eastern Europe and the former Soviet Union. The sudden changes traumatized the whole economy, with imports reduced by 50% and the gross domestic product (GDP) decreased by 30% (ref. 3). Even the general nutrition of the population suffered; per capita caloric intake was reduced by 24% (ref. 4). The ongoing US trade embargo with Cuba was tightened at the same time, worsening an already serious economic situation. The nation has slowly been rebuilding its economy, but the purchasing power of exports has still not reached the levels of the late 1980s.

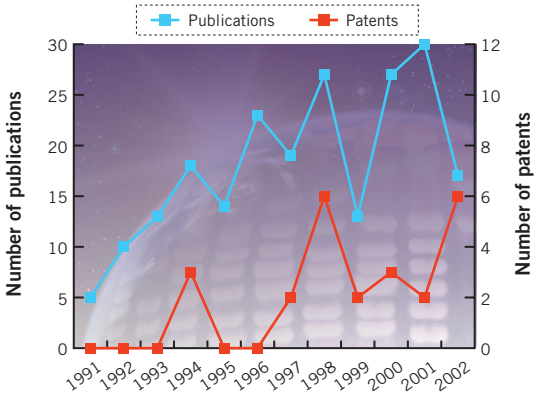

Figure 1 Cuban publications and USPTO patents in health biotechnology (1991–2002). Source: Publication data are from ref. 2. Patent data are from the USPTO.

Despite economic hardship, the government has continued to support health biotechnology. As one interviewee from a public research institution said, "There was a political will by the government to put money into this field [health biotechnology], despite a very difficult economic condition. When the Soviet Union collapsed, the economy touched bottom. Despite that, the Cuban government decided to construct institutes." In fact, the economic conditions called for the exploitation of domestic capacities, because the country lacked the resources to import solutions. Because they had already developed capacity in the field of health biotechnology, the field was viewed as a resource the country could use to maintain a healthy population. Given the uncertainties of success and long time lines that may be needed to bring products to market, the government's continued support for health biotechnology shows an unusual level of commitment to technological development.

Research institutes and universities. Public research institutions play a central role in

Table 1 Examples of Cuban health biotechnology products

Sector	Type	Application	Producer[a]
Vaccines	Purified meningococci	Meningitis B and C	Vacunas Finlay (FI)
	Recombinant hepatitis B surface antigen	Hepatitis B	Heber Biotec (CIGB)
	Synthetic Hib	Pneumonia and meningitis	Heber Biotec (CIGB)
Therapeutics	Recombinant streptokinase	Cardiovascular disease	Heber Biotec (CIGB)
	Recombinant IFN-α	Viral infections and oncological diseases	Heber Biotec (CIGB)
	Recombinant epidermal growth factor	Burns, ulcer healing	Heber Biotec (CIGB)
	Recombinant granulocyte colony-stimulating factor	Leukopenia, neutropenia	Heber Biotec (CIGB) and CIMAB (CIM)
	MAb to CD3	Organ transplant rejection	CIMAB (CIM)
	Recombinant erythropoietin-α	Anemia	CIMAB (CIM)
	Humanized MAb against epidermal growth factor receptor	Head and neck tumors	CIMAB (CIM)
	Ateromixol (PPG)	Anti cholesterol	Laboratorios Dalmer (CNIC)
Diagnostics	Miniaturized enzyme-linked immunosorbent assay kits	AIDS, blood certification, prenatal diagnosis	Tecnosuma Internacional (CIE)
	Radiolabeled mAbs targeting various cancer markers	Cancer imaging	CIMAB (CIM)
	Enzyme-linked immunosorbent assays	Syphilis, celiac disease	Heber Biotec S.A. (CIGB)

[a]Abbreviations of associated research institutions are in parentheses: CIE, Center for Immunoassays; CIGB, Center of Genetic Engineering and Biotechnology; CIM, Center for Molecular Immunology; CNIC, National Center for Scientific Research; FI, Finlay Institute.

Illustration by R. Henretta

Box 1 World's first vaccine containing a synthetic antigen

At the end of the 1970s, there was an outbreak of meningitis infection by *Neisseria meningitidis* serogroup B in Cuba. The high rate of meningitis B infection threatened previous achievements in controlling the child mortality rate, and no vaccine was available worldwide for this serogroup. In response to the public health crisis, the government created a multidisciplinary, multi-institutional group to develop a vaccine candidate. This group, now located in the Finlay Institute, developed a vaccine candidate in 1985, which was subsequently proven effective. **Figure 2** illustrates how the incidence of the disease started to decline once the clinical trials of the vaccine were initiated. Cuba has patented this vaccine in several countries, including the United States.

More recently, the Synthetic Antigen Laboratory at the University of Havana has played a leading role in developing the world's first human vaccine with a synthetic antigen[13]. The vaccine protects against *Haemophilus influenzae* type b (Hib) infection, which often leads to pneumonia and meningitis in children under the age of 5. Made with a chemically produced antigen instead of fermented bacterial culture, it is much cheaper to produce and is considered safer than vaccines coming from living organisms. The innovative technology was first developed in collaboration between the University of Havana and the University of Ottawa (Ottawa, ON, Canada), and was jointly patented. They will waive any royalties from the sale of the vaccine in Cuba or in epidemic situations in developing countries.

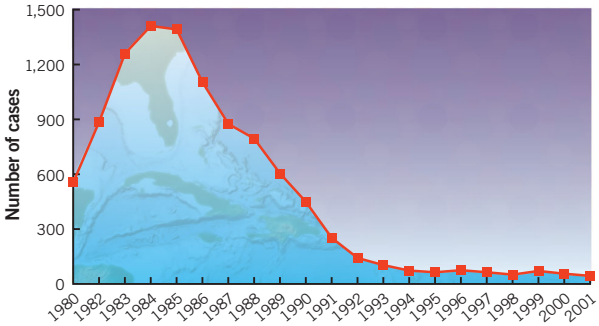

Figure 2 Incidence of meningitis in Cuba.

Cuba's health biotechnology sector. They typically focus on relatively, well-defined fields, such as immunology, tropical medicine, immunoassays or vaccines. Most of them were established from the late 1980s to the mid-1990s. Some of the institutions are directly under the control of the Council of State, which allows close ties to the central decision-making powers of the country. Many of the institutions are concentrated in the western part of Havana and are a part of the West Havana Scientific Pole. The Pole is a cluster of research institutions, higher education institutions and hospitals that were linked in the early 1990s in an attempt to encourage closer integration of science, education and health.

The public institutions are heavily involved in research and development activities. Their scientists published almost all of the Cuban health biotechnology papers that appeared in the internationally peer-reviewed journals from 1991 to 2002 (ref. 2), and the institutes also hold almost all of the Cuban patents in this field. The Centre of Genetic Engineering and Biotechnology (CIGB, Havana) is the largest of the health biotechnology institutions, and from 1991 to 2002 its researchers published over 55% of all the Cuban papers in health biotechnology[2].

Many of the institutions have what has been called the whole cycle or the closed cycle. They cover the gamut from the research realm, through development, production, quality control and commercialization of the end products. Several of the institutions have commercial arms, often in the form of an associated company. For example, Heber Biotec (Havana), the commercial arm of CIGB, sells products to more than 40 countries. Laboratorios Dalmer (Havana) markets products for the National Centre for Scientific Research (Havana), which focuses on natural products and nanotechnology. Vacunas Finlay (Havana) sells for the Finlay Institute (Havana), which focuses on vaccines, and CIMAB (the commercial arm of the Center of Molecular Immunology) does the same for the Center of Molecular Immunology (CIM, Havana), which focuses on monoclonal antibodies (mAbs) and cancer vaccines. These commercial entities carry out activities more commonly associated with private firms in other countries.

Cuba's universities have played a strong role in training experts for health biotechnology. Since the 1959 revolution, the educational level of the country has been raised substantially, giving it a highly qualified labor force. The educational level of Cuba's labor force at the end of the 1990s was almost equal to that of the Organisation for Economic Cooperation and Development (Paris) countries. It was actually higher than that of some 'emerging' economies, like Taiwan and Chile, even though they had considerably higher GDPs per capita[5]. In the early days of the health biotechnology development, Cubans used to go abroad to complete their education. However, the nation's universities have grown and are providing extensive training in the health biotechnology sector, to the point that there is much less need for a foreign education.

It is expensive to develop research infrastructure in health biotechnology, and the policy in Cuba has been to place the sophisticated research equipment in the public research institutes. During the Special Period, the universities suffered more cutbacks than the research institutions in the health biotechnology sector, and some university centers struggled to do research. Research collaboration between the universities and the research institutions has been encouraged, and some university institutions have made impressive contributions to health biotechnology. For example, researchers from the Faculty of Chemistry at the University of Havana made a leading contribution in the development of the synthetic *H. influenzae* type b vaccine (**Box 1**). Universities and research institutions also collaborate in the research training of students.

Health system. After the revolution, a central goal of the Cuban government was to improve the health of the population, and it established a health system with universal access. The health status of Cubans has improved substantially since 1959, and they enjoy a life expectancy of 76.7 years[6], one of

Illustration by R. Henretta

the longest in the Americas. The main driving force for the health biotechnology sector in Cuba has been to improve the health of Cubans, and the meningitis vaccine is a good example. The government's funding of both the development of health biotechnology products and the country's health delivery system provides incentives to focus on cost-effective health approaches, such as vaccines. Although the health biotechnology sector is oriented mainly toward Cuban health needs, exports are rising.

The health sector in Cuba is heavily involved in clinical trials, and many clinicians are intimately involved in the whole research process. For example, the research institute, Pedro Kourí Institute in Tropical Diseases (Havana), incorporates a hospital and plays a leading role in the evaluation and clinical trials for all Cuban vaccines. The tight integration of research with the health system and the Cuban health biotechnology sector encourages the creation of innovative products. A research director at a public research institute said, "We have feedback from the clinical trials to the lab. This is not a linear process. The cycle is a good ground for innovative thinking. It has definitely improved our products." The health sector is therefore not only a recipient of innovation but actively promotes it as well. The system has also played an important role in disseminating information about health biotechnology products. An extensive network of family doctors provides education about new products to the general public and explains their use and effectiveness. They thereby encourage the acceptance of local health biotechnology.

The general public. Research is lacking on the public's role in health biotechnology in Cuba, so it is difficult to present generalizing statements on the opinion of the general public. There seems, however, to be support for and pride about health biotechnology development in Cuba. This was evident during interviews with the experts from the health biotechnology sector but was echoed when talking to people from different walks of life in Havana. The support of the general population is also reflected in their willingness to take part in clinical trials of Cuban health biotechnology products. With a steady stream of new products in the pipeline, having a population that supports health biotechnology is a necessary asset.

Main challenges for development

Because Cuba's political system is not based on capitalism, the country must find novel ways of encouraging innovation, licensing and commercialization that can be reconciled with its socialist aims. The country's fiscal difficulties, limited access to international credit, large debt burden and isolation from the United States—the world's largest, richest and most developed biotechnology sector—limit growth of the Cuban sector. In addition, the US' policy of excluding Cuba from the international community limits the access of Cuban scientists to equipment, reagents and materials, and their ability to exchange ideas and information with non-Cuban colleagues. Those scientists that emigrate from the island are also less likely to return because of the political and/or economic situation.

Need to improve time lines and commercialization. To enhance competitiveness and productivity, the sector needs to make improvements, for example, by speeding product development so that therapies, vaccines and other applications can enter the market more rapidly. The involvement of public research institutions in diverse activities of health biotechnology may make it easier to coordinate and improve efficiencies.

The exceptional development of the country's biotech sector is due to the government's far-sighted and continued commitment to health, education and science.

There is also a need for Cuba to foster additional international commercialization. The interviews for this study indicated that there are some in the country who are critical of international commercialization and licensing of their technology, and there is an ongoing challenge to conduct market-oriented activities within a socialist system. As a Cuban expert involved in commercialization at a Cuban public research institute stated, "Capitalist organization is foreign to us, as is the whole sense of the venture capital. It is hard to understand, and we have to be innovative in fitting it with our structure… our business model. We have to think differently."

Lack of funding and the US trade embargo. Despite strong government commitment, Cuba's health biotechnology sector faces a lack of financial resources. The economic conditions in Cuba are problematic, and the government does not have an impressive track record of building a strong and diversified economy[7]. Limited access to international credit has made it harder for the country to engage in ambitious restructuring schemes, such as those taking place in Eastern Europe, and Cuba continues to struggle to pay off its debt. The US trade embargo has limited the economic options for Cuba, including development of the health biotechnology sector. For example, Cuba is forced to import research equipment from countries other than the United States—a situation that not only consumes time but adds to the cost. Another challenge imposed by the poor Cuba-US relations is the increasing difficulty that Cuban scientists face obtaining visas to enter the United States to attend conferences and other related activities. Also, even though the US Treasury Department has as of April 2004 officially permitted papers from embargoed countries to be edited and published in US journals, the uncertainties of the embargo have made it difficult for Cuban papers to be accepted in US journals[8]. The embargo therefore restricts the knowledge flow involving Cuban scientists in the international scientific community and adds costs, because Cubans have to attend conferences that are held in countries other than the United States. Another challenge is the dominance of US firms in the global health biotechnology sector. This may limit the options for Cuba in developing joint ventures, strategic alliances and licensing of their technologies.

Brain drain. Cuban health biotechnology development has also suffered the loss of some of their researchers and other experts, who have left the country. This is a problem faced by several developing nations, and there is no indication that this loss is any larger in Cuba than in any other developing countries. The brain drain in Cuba has, however, often political elements and consequences. For a perspective of a Cuban émigré see Jose de la Fuente[9]. As a result Cuban expatriates are less likely to contribute towards Cuban health biotechnology than those from other countries do for their former homelands.

Conclusions

The three main pillars of Cuban society after the revolution were health, education and science. The exceptional development of the country's biotech sector is due to the government's far-sighted and continued commitment to these principles. Because of external conditions, health care biotechnology in Cuba has had to show a greater level of self-sufficiency than elsewhere; thus, among and

Box 2 Learning through interferon

In November 1980 the President of Cuba, Fidel Castro, became aware that interferon-α 2b (IFN-α) was a promising candidate for cancer treatment. He received an invitation to send a researcher to the cancer institute of a leading American oncologist, Randolph Lee Clark, to learn about the clinical uses of IFN-α. In the wake of this experience, a decision was made to send six researchers to the Department of Virology, Central Public Health Laboratory, Helsinki, Finland, run by Kari Cantell, to learn how to make IFN-α. After they had obtained their training, a special laboratory was set up in a small house in Havana to see if they could reproduce the Finnish results and produce IFN-α in Cuba. Fidel Castro was very much involved with the project and visited the researchers every day. By late May 1981, the research group had managed to make the first IFN-α in Cuba. The accomplishment of producing IFN-α in such a short time was very impressive and energized research efforts in this field. Even though IFN-α has not become the magic bullet in treating cancer as originally hoped, it was important in boosting learning and the confidence of Cubans in biotechnology. The experience of learning reverse engineering was a first step leading to their own innovations and knowledge development.

within its research institutions, knowledge sharing and cooperation must be maximized and competition for resources and internal turf wars over rights to projects minimized. At the same time, Cuba must continue to promote links with external markets and outside expertise; it can do so in the knowledge that its biotech sector is the envy of the developing world and a great source of national pride. Four major lessons in building a biotech sector without the presence of a source of venture capital are evident from our analysis of the Cuban health biotechnology sector.

Long-term governmental vision and policy coherence. A key to the Cuban success in the field of health biotechnology is the government's long-term vision to support health biotechnology, even though that investment is not likely to produce benefits in the short term. It takes a long time to develop and test health biotechnology products and processes, and many promising leads turn out to be ineffective or have harmful side effects.

The Cuban government started to support health biotechnology in the early 1980s, and it did not waver in support during the economic hardship in the 1990s. Such policy coherence is essential for risky, science-intensive fields, such as health biotechnology.

Promotion of domestic integration to spur innovation. Cubans have promoted health biotechnology by developing a research infrastructure and have supported this with strong health and education systems. As the health biotechnology sector advanced, it had access to an educated workforce and a well-functioning public health system, both of which contributed to innovation.

There are strong linkages between Cuba's health biotechnology research system and its health system. The major hospitals are partners in the health biotechnology cluster, and the cluster has therefore both users and producers of health biotechnology. This means that the scientific potential can be communicated to people who have firsthand experience with local health problems. Knowledge flow between these institutions is important for innovation, and the health system is not only the recipient of innovation but also a contributor. By comparison, the relative weakness of public health systems in most developing countries limits their ability to produce health biotechnology innovations.

> Knowledge sharing among and within the research institutions is an important feature of the Cuban system.

Knowledge sharing among and within the research institutions is an important feature of the Cuban system. Many public research institutes house diverse health biotechnology activities, including research, development and production. Information sharing can encourage coordination and linkages and contribute toward success in the field. The Cubans have also been at the forefront of promoting cluster development, as exemplified by the West Havana Scientific Pole.

Capitalizing on international linkages. International linkages have also been a pivotal part of Cuban health biotechnology development. International education played a central role in building expertise in the sector, as can be seen in the example from the IFN-α project (**Box 2**). Learning from this project helped in other projects.

There was a surge of Cubans obtaining foreign training around 1980 when biotechnology was a new field. Many studied at the pioneering life science institutions in Western Europe and the United States, including the Curie Institute (Paris), the Pasteur Institute (Paris), Heidelberg University (Heidelberg, Germany) and Harvard University (Cambridge, MA, USA)[10]. This helped shape the thinking of some of Cuba's current leaders of health biotechnology research. As the sector has advanced, the knowledge flows have become more varied and are increasingly both to and from Cuba.

Even at the commercial level, Cubans are involved in international collaboration with private sector firms around the world. For example, Finlay Vacunas has an agreement with GlaxoSmithKline (Brentford, UK) to produce and distribute the meningitis vaccine in Europe and North America. The United States has even allowed the company to sell the drug on the US market, so long as it passes clinical trials. CIGB has set up strategic alliances with the Indian firm, Panacea Biotec (New Delhi), to manufacture hepatitis B vaccine, and CIMAB, the commercial arm of CIM, has established a joint venture, called CIMYM (a joint venture between CIM and the Canadian firm YMBiosciences (Mississauga)), to develop and market cancer therapeutics. They recently made an agreement, approved by the US Treasury Department, with US firm CancerVax (Carlsbad, CA) to undertake joint development and licensing of Cuban cancer vaccines[11].

Through these linkages, Cubans have gained access to markets, capital and commercialization expertise. Sometimes it has been challenging for Cubans to adapt their socialist system to the capitalist world of modern biotechnology. They have modified their legislation to accommodate flexibility in foreign investment, with the Foreign Investment Law that was approved by the National Assembly in 1994 (ref. 12). They have also granted the research institutions increased flexibility and autonomy by permitting them to use a portion of the hard currency they earn through the foreign enterprises.

Tapping into national pride. National pride and the impetus to prove that the political system in Cuba works well are other important aspects of the Cuban biotechnology system. If there is a sense that the health

system is slipping, the government is motivated to take action to solve the problem.

At the individual level, health biotechnology activities fuel pride in Cubans, who see their poor country making advances in such a science-intensive sector as health biotechnology. As one Cuban scientist said, "I feel that as a product of the Cuban system I have to give something back. I feel very proud that, thanks to my work, people that are sick are treated. We should use our principles in the professional life and apply our knowledge." This is an indication of a national approach to health that is more focused on community goals and the operation of the whole system than on individuals and their assets. It is also indicative of how political issues and social norms can have extensive influences on innovative behavior.

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